

Impact of gastrointestinal physiology on drug absorption in special populations - an UNGAP review

Stillhart, Cordula; Vučićević, Katarina; Augustijns, Patrick; Basit, Abdul W.; Batchelor, Hannah; Flanagan, Talia R.; Gesquiere, Ina; Greupink, Rick; Keszthelyi, Daniel; Koskinen, Mikko; Madla, Christine M.; Matthys, Christophe; Miljuš, Goran; Mooij, Miriam G.; Parrott, Neil; Ungell, Anna-lena; De Wildt, Saskia N.; Orlu, Mine; Klein, Sandra; Müllertz, Anette

DOI:

[10.1016/j.ejps.2020.105280](https://doi.org/10.1016/j.ejps.2020.105280)

License:

Creative Commons: Attribution (CC BY)

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Stillhart, C, Vučićević, K, Augustijns, P, Basit, AW, Batchelor, H, Flanagan, TR, Gesquiere, I, Greupink, R, Keszthelyi, D, Koskinen, M, Madla, CM, Matthys, C, Miljuš, G, Mooij, MG, Parrott, N, Ungell, A, De Wildt, SN, Orlu, M, Klein, S & Müllertz, A 2020, 'Impact of gastrointestinal physiology on drug absorption in special populations - an UNGAP review', *European Journal of Pharmaceutical Science*, vol. 147, 105280. <https://doi.org/10.1016/j.ejps.2020.105280>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.



Impact of gastrointestinal physiology on drug absorption in special populations—An UNGAP review

Cordula Stillhart^a, Katarina Vučićević^b, Patrick Augustijns^c, Abdul W. Basit^d, Hannah Batchelor^e, Talia R. Flanagan^f, Ina Gesquiere^c, Rick Greupink^g, Daniel Keszthelyi^h, Mikko Koskinenⁱ, Christine M. Madla^d, Christophe Matthys^j, Goran Miljuš^k, Miriam G. Mooij^{l,m}, Neil Parrottⁿ, Anna-Lena Ungell^o, Saskia N. de Wildt^{g,p}, Mine Orlu^d, Sandra Klein^q, Anette Müllertz^{r,*}

^a Formulation & Process Sciences, F. Hoffmann-La Roche Ltd., Basel, Switzerland

^b Department of Pharmacokinetics and Clinical Pharmacy, Faculty of Pharmacy-University of Belgrade, Vojvode Stepe 450, Belgrade 11221, Republic of Serbia

^c KU Leuven, Belgium

^d UCL School of Pharmacy, University College London, United Kingdom

^e School of Pharmacy, Institute of Clinical Sciences, University of Birmingham, Robert Aitken Building, Edgbaston, B15 2TT, United Kingdom

^f Pharmaceutical Development, UCB Biopharma SPRL, Braine - l'Alleud, Belgium

^g Department of Pharmacology-Toxicology, Radboud University Medical Center, the Netherlands

^h Division of Gastroenterology-Hepatology, Department of Internal Medicine, NUTRIM, Maastricht University Medical Center, the Netherlands

ⁱ Orion Corporation, Orion Pharma, Finland

^j Clinical and Experimental Endocrinology, KU Leuven, Belgium

^k Department for Metabolism, Institute for the Application of Nuclear Energy-University of Belgrade, Serbia

^l Radboud University Medical Center, Department of Pharmacology and Toxicology, Nijmegen, the Netherlands

^m Leiden University Medical Centre, Department of Pediatrics, Leiden, the Netherlands

ⁿ Pharmaceutical Sciences, Roche Pharma Research and Early Development, Roche Innovation Centre Basel, Basel, Switzerland

^o Development Sciences, New Medicines, UCB Biopharma SPRL, Braine - l'Alleud, Belgium

^p Intensive Care and Department of Pediatric Surgery, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands

^q Department of Pharmacy, University of Greifswald, Germany

^r Department of Pharmacy, University of Copenhagen, Denmark

ARTICLE INFO

Keywords:

Oral drug absorption
Special populations
Gastrointestinal tract physiology
Biopharmaceutics
Oral bioavailability

ABSTRACT

The release and absorption profile of an oral medication is influenced by the physicochemical properties of the drug and its formulation, as well as by the anatomy and physiology of the gastrointestinal (GI) tract. During drug development the bioavailability of a new drug is typically assessed in early clinical studies in a healthy adult population. However, many disease conditions are associated with an alteration of the anatomy and/or physiology of the GI tract. The same holds true for some subpopulations, such as paediatric or elderly patients, or populations with different ethnicity. The variation in GI tract conditions compared to healthy adults can directly affect the kinetics of drug absorption, and thus, safety and efficacy of an oral medication.

This review provides an overview of GI tract properties in special populations compared to healthy adults and discusses how drug absorption is affected by these conditions. Particular focus is directed towards non-disease dependent conditions (age, sex, ethnicity, genetic factors, obesity, pregnancy), GI diseases (ulcerative colitis and Crohn's disease, celiac disease, cancer in the GI tract, Roux-en-Y gastric bypass, lactose intolerance, *Helicobacter pylori* infection, and infectious diseases of the GI tract), as well as systemic diseases that change the GI tract conditions (cystic fibrosis, diabetes, Parkinson's disease, HIV enteropathy, and critical illness).

The current knowledge about GI conditions in special populations and their impact on drug absorption is still

* Corresponding author.

E-mail addresses: cordula.stillhart@roche.com (C. Stillhart), katarina.vucicevic@pharmacy.bg.ac.rs (K. Vučićević), patrick.augustijns@kuleuven.be (P. Augustijns), a.basit@ucl.ac.uk (A.W. Basit), h.k.batchelor@bham.ac.uk (H. Batchelor), Talia.Flanagan@UCB.com (T.R. Flanagan), ina.gesquiere@kuleuven.be (I. Gesquiere), Rick.Greupink@radboudumc.nl (R. Greupink), daniel.keszthelyi@maastrichtuniversity.nl (D. Keszthelyi), mikko.koskinen@orionpharma.com (M. Koskinen), christine.madla.16@ucl.ac.uk (C.M. Madla), christophe.matthys@uzleuven.be (C. Matthys), goranm@inep.co.rs (G. Miljuš), M.G.Mooij@lumc.nl (M.G. Mooij), neil.john.parrott@roche.com (N. Parrott), AnnaLena.Ungell@ucb.com (A.-L. Ungell), Saskia.deWildt@radboudumc.nl (S.N. de Wildt), m.orlu@ucl.ac.uk (M. Orlu), Sandra.Klein@uni-greifswald.de (S. Klein), Anette.mullertz@sund.ku.dk (A. Müllertz).

<https://doi.org/10.1016/j.ejps.2020.105280>

Received 2 November 2019; Received in revised form 10 February 2020; Accepted 24 February 2020

Available online 25 February 2020

0928-0987/ © 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

limited. Further research is required to improve confidence in pharmacokinetic predictions and dosing recommendations in the targeted patient population, and thus to ensure safe and effective drug therapies.

ABC	ATP-binding cassette
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BMI	Body-mass index
CD	Crohn's disease
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
C _{max}	Maximum plasma concentration
CYP	Cytochrome P450
FDA	Food and Drug Administration
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
H. pylori	Helicobacter pylori
HIV	Human immunodeficiency virus
IBD	Inflammatory bowel disease
ICH	International Conference for Harmonization
OATP	Organic anion transporting polypeptides
PARKD	Parkinson's Disease
PBPK	Physiologically-based pharmacokinetic
PEG	Polyethylene glycol
P-gp	P-glycoprotein
PK	Pharmacokinetic
popPK	Population pharmacokinetic
RYGB	Roux-en-Y gastric bypass
T1DM	Type-1 diabetes mellitus
T2DM	Type-2 diabetes mellitus
T _{max}	Time to maximum plasma concentration
UC	Ulcerative colitis
UGT	5'-diphospho-glucuronosyltransferase

1. Introduction

Oral dosing is the preferred route of administration as it is convenient and safe for most populations (Stewart et al., 2016). Upon oral administration, the drug is passing through the stomach to the small intestine where most of the drugs are absorbed. Poorly absorbed drugs, or drugs in modified release formulations will pass to the colon, where further absorption can occur. During the development of new medicines, the absorption behaviour of oral compounds is usually studied in healthy adults. However, the morphology and physiology of the gastrointestinal (GI) tract is influenced by multiple factors such as age, sex, ethnicity, genome, or the disease state of the treated patient. These factors can significantly alter the kinetics of drug absorption, as well as the total amount of drug absorbed, thereby changing the pharmacokinetics of a drug and possibly its effect compared to the observed behaviour in healthy adults.

The main physiological parameters that are often altered in patients compared to healthy populations are the gastric emptying rate and pH, transit times across the different intestinal segments, intestinal surface area, epithelial permeability, as well as intestinal enzyme and transporter expression. Further differences may be observed with regard to the volume and composition of luminal fluids and of the intestinal microbiota (Fleisher et al., 1999; Bai et al., 2016; Effinger et al., 2019).

The possible interaction between co-administered drugs (polypharmacy), between the drug and the excipients in its formulation, as well as the drug-mediated effect on the GI tract physiology further add to the complexity of drug absorption. An example is cyclosporine A, which is known to inhibit cytochrome P450 (CYP) isoenzymes, particularly CYP 3A4, 2D6, and 2C19 (Niwa et al., 2007); however, it has

also shown a potential effect on the small intestinal transit time (Buggins et al., 2007), suggesting a rather complex impact of cyclosporine A on the overall GI tract physiology.

The dosage forms are typically selected based on the biopharmaceutical behaviour anticipated in healthy adults and are in many cases used in patients irrespective of the physiological differences between these populations. These differences may strongly influence the drug performance and result in large variability in exposure, which in turn could result in reduced efficacy, higher incidence of adverse events, and/or impaired compliance during clinical use. Thus, the characteristics of the targeted population and possible differences in GI tract physiology compared to healthy adults have to be considered from the outset start of drug and formulation development.

During drug development physiologically based pharmacokinetic (PBPK) modelling software tools are increasingly used for predicting pharmacokinetic (PK) profiles or performance of dosage forms. The strengths of these models lies in the possibility to include altered physiological parameters to mechanistically predict drug disposition. A major limitation of such models is, however, the lack of quantitative data describing variation in all processes involved and the validation of these models (Peters et al., 2016).

Recently, several reviews on the relation between drug absorption and systemic diseases (Hatton et al., 2019) or GI diseases and disorders (Effinger et al., 2019; Hatton et al., 2018), have been published and provide a good overview of these areas. In contrast, this review aims to cover changes in oral drug absorption in both non-disease and disease related conditions that can influence the physiology of the GI tract, and thereby absorption of drugs. After a short introduction to GI physiology in the healthy adult, the present review is divided into three sections, including non-disease dependent conditions, diseases in the GI tract, and systemic diseases, all with the aim of providing a comprehensive overview of the influence of different GI conditions on drug absorption.

2. GI tract physiology in healthy adults

The GI tract physiology in healthy adult subjects and its impact on oral drug absorption has been extensively studied in the past decades and comprehensive reviews can be found in the literature (Bergstrom et al., 2014; Dressman and Reppas, 2010). A brief overview of the main physiological parameters of the human GI tract is presented here.

The pH of luminal fluids is acidic in the stomach (pH 1.5–3.5), and increases to approximately pH 5–6 in the duodenum and pH 7–8 in the distal jejunum and ileum, before dropping to pH 6 in the colon with high interindividual variability (Evans et al., 1988; Koziolok et al., 2015). The pH affects the degree of ionization of drug molecules, influencing their dissolution and permeation behaviour, as well as the performance of some drug delivery systems, such as modified-release formulations.

The gastric emptying time, measured by magnetic resonance imaging as the time to get back to fasted gastric volumes, is approximately 45 min after a glass of water (240 mL) and more than 6 h after a standardized Food and Drug Administration (FDA) high-caloric breakfast (Koziolok et al., 2014; Mudie et al., 2014). The small intestinal transit time has been reported to be relatively constant between 4.3 and 4.6 h, whereas the colonic transit time is very variable between ~18 and 34.2 h (Becker et al., 2014; Sarosiek et al., 2010; Maharaj and Edgington, 2016).

Intestinal absorption can occur through passive permeation (paracellular or transcellular) or active uptake via intestinal transporters

depending on both the physicochemical characteristics of the drug and the properties of the intestinal membrane in different regions of the GI tract. Polar molecules pass through the passive paracellular route depending on their molecular size and charge, while more hydrophobic molecules tend to be absorbed via the transcellular route. Since the epithelial membrane composition, surface area, and pore size, are varying along the GI tract, polar molecules tend to be absorbed in the upper small intestine while hydrophobic molecules can penetrate across the membrane throughout the intestine (Sarosiek et al., 2010).

Reviews of intestinal transporter expression and specificity have been published recently (Drozdziak et al., 2014; Estudante et al., 2013). Some uptake transporters (monocarboxylate transporter 1 and organic cation transporter 1) are expressed along the whole GI tract (Sjoberg et al., 2013) while others are located in a specific region: peptide transporter protein 1 mainly in the jejunum and organic anion transporting polypeptides 2B1 (OATP2B1) mainly in the colon (Sjoberg et al., 2013). Overall the expression of efflux transporters, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug-resistance-associated protein 2, increases from the proximal to the distal small intestine (Peters et al., 2016; Gutmann et al., 2005; Berggren et al., 2007), which is opposite to the expression of cytochrome P450 enzymes being highest in the duodenum/jejunum (Peters et al., 2016; Stappaerts et al., 2013).

The volume of GI fluids determines the local drug concentrations in the GI tract, and thus, it affects the dissolution behaviour as well as the driving force for permeation. Several studies using magnetic resonance imaging can be found in the literature (Grimm et al., 2018; Mudie et al., 2014; Perez de la Cruz Moreno et al., 2006; Schiller et al., 2005). In the fasted stomach, resting gastric fluid volumes between 25 and 45 mL have been reported with significant interindividual variability (Grimm et al., 2018; Mudie et al., 2014; Schiller et al., 2006). In contrast, the volume in the fed state is dependent on the volume of the ingested food, and the time after ingestion. In the small intestine the fasted state volume has been reported to be 43 ± 14 mL (range 5–159 mL), which was non-evenly distributed in small pockets (Mudie et al., 2014). In the ascending colon, mean fluid volumes of 7 to 22.3 mL were measured in the fasted state and 29.9 mL the fed state, respectively (Murray et al., 2017; Diakidou et al., 2009).

The composition of bile salts and pancreatic enzymes can affect the solubility and dissolution rate especially of hydrophobic drugs in the gut. The overall composition of intestinal fluids changes during intestinal transit due to digestion and absorption processes, as well as the secretion of bile and pancreatic fluids into the intestinal lumen. In the fasted state, the concentration of bile salts ranges from 2.5 to 5.9 mM in the duodenum and from 1.4 mM to 5.5 mM in the jejunum. Only few studies have determined the regional bile salt level in the fed state, and reported values between 3.6 and 24.0 mM in the duodenum and 4.5 and 8.0 mM in the jejunum. The large variability also reflects the effect of different food types ingested (Bergstrom et al., 2014). In the fasted state, the rank order of relative bile salt concentration in the duodenum was reported as follows: taurocholic acid > glycocholate > glycochenodeoxycholate > glycodeoxycholate > taurochenodeoxycholate > taurodeoxycholate. The concentration of cholic acid, tauroursodeoxycholate, chenodeoxycholic acid, and deoxycholic acid was less than 1% of the total bile salts (Perez de la Cruz Moreno et al., 2006). Other minor components of luminal fluids can be found in Diakidou et al. (2009) and Perez de la Cruz Moreno et al. (2006). Interestingly, the relative composition of bile salts is similar between fasted and fed state in the upper GI tract as well as in the lower bowel (Diakidou et al., 2009; Perez de la Cruz Moreno et al., 2006; Riethorst et al., 2016). However, some disease states have been associated with erroneous synthesis of bile acids resulting in different relative concentrations compared to healthy subjects (Sundaram et al., 2008).

The healthy human gut is populated with billions of microbes, the microbiome, that contributes to a dynamic relationship between immune and metabolic function. The weight of the intestinal microbiome

amounts to around 1.8 kg in adults and every individual has a unique mix of microbial species. The diversity of microbes within a given body can be defined as the number and abundance distribution of distinct types of organisms. An imbalance in this diversity has been linked to several human diseases, such as obesity and inflammatory bowel disease (Human Microbiome Project Consortium, 2012). In addition, many bacteria in the gut microbiome have been shown to metabolise drugs, with potential consequences for the pharmacokinetics and effect of the drug (Zimmermann et al., 2019). A large database on the human microbiome, including a variety of species for healthy and diseased humans can be found in the Human Microbiome Project Consortium report (Human Microbiome Project, 2012).

3. Non-disease dependent conditions

3.1. Paediatric age groups

The paediatric population is a diverse 'special' population as it includes sub-populations including pre-term and term neonates, infants, children and adolescents. The impact of age on drug absorption has been reviewed recently for children (Guimaraes et al., 2019; Johnson et al., 2018) and neonates (Neal-Cluever et al., 2019; Somani et al., 2016). Both the rate and the extent of absorption of drugs in children is different than in adults with the greatest differences from the adult being observed in neonates (Batchelor et al., 2014). The difficulties of extrapolation of oral absorption data from adult data into paediatric populations is further complicated by the dose adjustment made for the population. For a long time, the standard approach for dose adjustments was based on the weight or by body surface area of the patient with no regard to the overall absorptive capacity of the paediatric intestine and age-related changes of oral drug absorption processes in the intestine. Since more recently, paediatric dose adjustment based on allometric concepts and ontogeny is considered more appropriate, but to date no final consensus on the suitability of different methodologies for dose adjustment in children has been reached.

When dosing oral medicines it is important to recognise that most oral processes are present from birth (rooting, lip, lateral tongue, mouth opening, biting, and emerging chewing behaviours) (Sheppard and Mysak, 1984). However, functionality is not fully matured: e.g., oral syrups are incompletely swallowed when administered to neonates and infants (Klingmann et al., 2018).

Key findings from recent reviews on the ontogeny of oral drug absorption processes are presented in summary here and, where available, newer data is included (Mooij et al., 2012). In contrast to what has been echoed in multiple reviews, the gastric pH is only high directly after birth, likely due to buffering of remaining amniotic fluid, and rapidly decreases to pH 1 to 3 in children of all ages (Mooij et al., 2012). Collection of paediatric gastric fluids have shown pH values ranges from 2.0 to 2.7 in neonates and typically <3 in children and adolescents (Van Den Abele et al., 2018). The postprandial buffering effect of a milk-based diet in frequently-fed neonates results in a higher percentage of time at higher gastric pH.

The paediatric gastric emptying time is highly variable in children younger than 6 months and paracetamol absorption kinetics have revealed delayed gastric emptying in the first few days of life. Intestinal transit time is also slower in neonates and infants yet reaches adult values by the age of 2 years (Bonner et al., 2015).

To study the effect of age and feeding *in vitro*, simulated paediatric fasted- and fed-state gastric and intestinal fluids have been developed based on literature data to inform their composition, although the evidence-base is limited (Maharaj et al., 2016). The solubility of six drugs were evaluated in these new paediatric media and compared to values from adult simulated media; key differences in solubility were found for neonatal media where milk was a component. Typically, the differences in solubility were outside the nominal 80–125% bioequivalence criteria for neonatal media compared to adults (Maharaj et al.,

2016). Very recent work has shown that the total bile salt concentration in gastric fluids collected from neonates and infants was low with 31.2 and 9.2 μM , respectively; whereas higher values were found in children (99.5 μM) and adolescents (763.6 μM) (Van Den Abeele et al., 2018). Small intestinal pH has only been studied in older children and showed adult values; bile acid concentrations are reported to reach adult values around the age of 4 years. Pancreatic function appears to be sufficient in healthy neonates, independent of gestational age (Zoppi et al., 1972).

Drug absorption in the intestine may be affected by age-related changes in intestinal permeability, as well as activity of drug metabolizing enzymes and membrane transporters. Intestinal permeability is reported to be higher in neonates compared to adults with factors relating to the three-dimensional shape of the intestinal mucosal surface as well as the high nutritional need of this sub-population (Bezerra et al., 1990). The ontogeny of intestinal and hepatic drug metabolizing enzymes and transporters, both impacting oral bioavailability, shows age-dependent and transporter-specific profiles (Brouwer et al., 2015; Mooij et al., 2016a; Mooij et al., 2016b; Mooij et al., 2016c; Cheung et al., 2019; van Groen et al., 2018). For example, hepatic ATP-binding cassette B1 (ABCB1) expression appears low at birth as compared to adults, but stable in the intestine. In contrast to the stable intestinal ABCB1 expression, OATP2B1 expression in the intestine appears higher in neonates than in older children and adults. By combining the existing physiological data from children across the paediatric life span and PK data of oral and intravenous administration, physiology based (population) PK studies aimed to elucidate the relative contribution of intestinal and hepatic drug metabolism during growth and maturation (Brussee et al., 2018a; Brussee et al., 2018b). While very informative, these models are still hampered by limited data on age-related physiological parameters, including intestinal drug metabolizing enzyme and transporter expression (Kodidela et al., 2017).

The impact of food and nutrition can influence the absorption of drugs as the diet particularly in neonates and infants with milk-based feeding is different to that in adults (Batchelor et al., 2018; Karkossa et al., 2017). Not only buffering of gastric pH by milk, as discussed above, but dietary conditions, may also change drug metabolizing enzyme and maybe transporter maturation, as for example CYP 1A2 and CYP 3A4 activity appears to be higher in formula fed than in breast-milk fed neonates (Blake et al., 2006). However, it is not yet clear if this is caused by the presence of an inducer in formula or an inhibitory factor in breast milk. In young children, manipulations with drugs (i.e., crushing, dissolving tablets) or co-administering with food to enhance ingestion by children may affect drug bioavailability.

In conclusion, gaps in knowledge are related to the composition and volume of fluids present in the small intestine, the expression of intestinal transporters and metabolizing enzymes, and methods to understand permeability in paediatric intestine and pathways relevant to intestinal wall metabolism. Major knowledge gaps were identified in the most vulnerable groups of neonates and infants under 6 months of age. In addition, there is a critical need for PK data from these young populations to better understand the implications of GI differences on the absorption of drugs.

3.2. Advanced age

As age advances, the GI tract undergoes a variety of morphological and functional changes that result in a general decline in bodily function. The complex deterioration of normal GI parameters can therefore compromise effective drug absorption in the elderly population, who is often subject to polypharmacy. The impact of advanced age on GI physiological factors including GI transit, pH, expression of metabolizing enzymes and membrane transporters, permeability and the microbiome are limited (Khan and Roberts, 2018), but studies have demonstrated minor differences when compared with healthy adults (Brognia et al., 1999; Carrion, 2017; Fakhoury et al., 2005; Holt, 2018;

Russell et al., 1993).

There is an important interaction between drug absorption and nutritional practice prevalent in the older population. For example, the limited fluid intake in the geriatrics in particular has the potential to influence the intestinal absorption process. In addition, the thirst sensation is diminished in elderly (Carrion, 2017; Kenney and Chiu, 2001). The consequence of the reduced fluid intake in the longer term, however, may be associated with the impaired drug absorption. Further research is required to generate evidence-based data to understand: (i) whether the alteration in thirst physiology is associated with changes in intestinal absorption and (ii) if it is associated, which drugs are subject to altered absorption profiles in older people with diminished thirst.

Nutritional intake is also subject to change at advanced age. Fibre-based enteral nutrition is often administered to improve bowel function in the elderly. Hence, age-related motility changes as a result or in combination with these formulations may elicit varying intestinal drug absorption profiles. More importantly, the geriatric population is the main user of thickening agents to manage dysphagia. The administration of a drug product mixed with thickening agents may present an unforeseen reason for changes in the bioavailability profile (McKinley et al., 2006).

Drug absorption in the GI tract should be investigated thoroughly in the presence of disease. The incidence of disease is higher in the elderly although this factor is rarely considered as the primary cause of variability in drug absorption as drug bioavailability may further be perturbed due to advanced age or a combination of both. Therefore, it is more complicated to understand the intestinal absorption profile of a drug in an older individual with a clinical condition.

Polypharmacy may further contribute to varied absorption in the intestine, for example due to drugs that increase the risk of constipation. As multi-morbidity, and consequently polypharmacy, is predominant in the elderly, the use of drugs with an effect on the GI pattern is more frequent than in younger subjects (Cichero, 2013; Petrini et al., 2019).

Overall, there is a lack of consensus regarding the independent effects of ageing on intestinal absorption due to: (i) the challenge in investigating the aged intestine that is free of disease; (ii) the lack of harmonisation in the applied methods and tools to study drug absorption from the intestine at old age and; (iii) the scattered approach in reporting the GI physiology related factors as the main drivers for drug absorption. Clinical studies including healthy elderly subjects should be encouraged to understand GI tract physiology and drug absorption in this population.

3.3. Sex differences

Men and women respond differently to medicines. These sex differences, however, have largely been neglected in the drug development arena. Many pharmaceutical scientists can attest that for decades, the default human model subject was a “70 kg Caucasian male” (Beery et al., 2011; Yoon et al., 2014). With the effort to overcome the disparity between sexes in biomedical research, the FDA and the National Institutes of Health mandated for the inclusion of women in clinical trials in the U.S. in 1993. Nonetheless, following the review of ten drugs that were withdrawn from the market from 1997 to 2000, it was found that withdrawal of eight of the ten drugs were due to greater risks of adverse effects in women (GAO, 2001). In addition, out of 67 new molecular entities approved by the U.S. FDA between 2000 and 2002, 25 compounds demonstrated significant sex-specific differences in PK and efficacy (Yang, 2009). Ignoring female participants in clinical trials has backfired and has resulted in the significant implications in women directly related to drug use. For example, only identified during post-market drug surveillance, women were more susceptible to next-day effects following the administration of the sedative zolpidem as drug elimination was slower in women than in men. The FDA subsequently recommended that immediate-release and extended-release

products were to reduce the dose from 10 mg to 5 mg and 12.5 mg to 6.25 mg respectively for women (Norman et al., 2017). In addition, women are also at a greater risk (50–70%) of experiencing adverse side effects (Rademaker, 2001), which may be directly linked to distinct GI physiological differences between the sexes.

Drug dissolution is often the rate limiting step in drug absorption, however, it was identified that fluid volumes in the stomach and small intestine (following the normalisation of body weight) were higher in men than in women (Gotch et al., 1957; Soldin and Mattison, 2009). In terms of gastric pH, the fasted state pH is higher in females than in males (2.79 ± 0.18 and 2.16 ± 0.09 , respectively), which may be attributed to reduced acid secretion and smaller sized female stomach (Feldman and Barnett, 1991; Phan et al., 2015). Lowered gastric acid secretion may influence drug ionisation and solubility of pH-sensitive drugs, thereby impairing absorption and consequently, oral drug bioavailability (Lahner et al., 2014).

With regards to motility, pre-menopausal women have a significantly longer gastric emptying time when compared with their male counterparts for solids and calorific liquids, however, in post-menopausal women, gastric emptying time decreases and becomes similar to that in men (Bennink et al., 1998). Variabilities in drug PK can be attributed to differences in gastric emptying time as a shorter absorption lag time of an enteric-coated aspirin tablet was demonstrated in males than females (Mojaverian et al., 1988; Fischer and Fadda, 2016). Colonic transit time is also significantly longer in women than in males (ascending colon: 13.3 ± 1.6 h; 8.9 ± 1.1 h and transverse colon: 13.7 ± 2.1 h; 8.7 ± 1.5 h; descending colon: 11.8 ± 1.6 h; 13.0 ± 1.7 h in women and men respectively) (Metcalf et al., 1987; Rao et al., 2009). The increased total intestinal transit time in women would have significant implications to oral drug bioavailability. The longer GI residence time for sustained-release dosage forms may facilitate enhanced drug absorption in women as demonstrated with the PK profile of an extended-release formulation of diltiazem, which was demonstrated to be sensitive to GI transit time (Zimmermann et al., 1999). This, however, may further be implicated by the regulation of intestinal membrane transporters and metabolising enzymes located in the GI mucosa.

CYP enzymes are responsible for the metabolism of a number of drug substrates of which CYP2C and 3A are most commonly expressed in the small intestine. For example, the oral bioavailability of verapamil (a CYP3A substrate) was higher in women than in men (Krecic-Shepard et al., 2000) due to higher intestinal CYP3A expression and activity (Tamargo et al., 2017). P-gp, the most studied efflux membrane transporter in the GI tract, has been shown to differentially affect oral drug absorption in males and females in the presence of so called “inert” excipients. A human study firstly identified that when co-formulated with 0.5 g polyethylene glycol 400 (PEG 400), the bioavailability of ranitidine (a P-gp substrate) significantly increased by 63% in males. In females, however, ranitidine bioavailability decreased by 8% when compared with the control (Ashiru et al., 2008). As aforementioned, the National Institute of Health mandated for women to be included in clinical trials in 1993. No such initiatives, however, have been implemented to investigate sex differences in pre-clinical research, i.e., cell and animal models. As early drug development often uses rats as animal models, the sex differences at a rodent physiological level can translate the oral drug performance in humans. A rat study was subsequently developed to explore the levels of P-gp along the gastrointestinal tract. Afonso-Pereira et al. identified that female rats displayed significantly higher relative P-gp expression levels than male rats throughout the small intestine (Afonso-Pereira et al., 2018). Excipients have since been identified to directly interact with the gene and protein expression of P-gp differently between males and females (Mai et al., 2017). The presence of PEG 400 and its potential interaction with P-gp was assessed for its gene and protein expression in the presence of a P-gp substrate (ranitidine and ampicillin), a non-P-gp substrate (metformin) and a P-gp inhibitor (cyclosporine A) in male and

female rats. The study showed that the bioavailability of ampicillin significantly increased ($p < 0.05$) in the presence of PEG 400 in male, but not female, rats. No sex differences were reported in the bioavailability of metformin in the presence of PEG 400. When formulated with a P-gp inhibitor (cyclosporine A), the bioavailability of ampicillin and ranitidine increased in males to a greater extent but showed no influence on metformin bioavailability. There is, therefore, a potential sex-specific effect of PEG 400 on the bioavailability of certain drugs due to the interaction of PEG 400 with the P-gp efflux transporter (Mai et al., 2018a). A recent study established an *in vitro* permeation model for the prediction of the *in vivo* sex-related influence of PEG 400 mediated by P-gp. The study identified a good *in vivo-in vitro* correlation for the influence of PEG 400 on the absorption of ranitidine in different segments of the small intestine which can predict drug bioavailability in human subjects (Mai et al., 2018b).

Advancements in the research has since revealed that the sex-specific influence of excipients on drug bioavailability is not limited to PEG 400 alone. Other solubilising excipients including PEG 2000, Cremophor RH 40, Poloxamer 188 and Tween 80 have shown to significantly increase ranitidine bioavailability, although this was only apparent in males but not in female rats (Mai et al., 2019). The effect of Span 20 was also studied on the oral bioavailability of ranitidine; although this solubilising agent was able to significantly increase ranitidine bioavailability, its effects were in a non-sex dependent manner. Consequently, sex-specific effects may be attributed to the presence of a polyoxyethylated group in PEG 2000, Cremophor RH 40, Poloxamer 188 and Tween 80, but not for Span 20.

Food intake has recently been discovered to affect the intestinal expression of P-gp in males and females. Dou et al. identified that relative P-gp levels decreased in all segments of the intestine (bar duodenum) in male rats following food intake. A fundamentally different outcome, however, was observed in female rats where the fed state resulted to a significant increase in P-gp expression in the small intestine. Specifically, a six-fold increase in jejunal P-gp expression occurred from the fasted to fed state in female rats. As such, intestinal permeation studies in an Ussing chamber showed that ganciclovir and ranitidine (both P-gp drug substrates) exhibited a sex difference in intestinal permeability from the fasted to fed state (Dou et al., 2018).

Adding further to the complexity of varying drug response between the sexes may be governed by the intestinal microbiome. The increasing number of microbiome studies have revealed the importance of the gut-brain axis namely the microbiota and the endocrine system with bacteria being able to produce hormones (e.g., serotonin and dopamine), respond to host hormones (e.g., oestrogen) and regulate the homeostasis of host hormones by inhibiting gene transcription (e.g., prolactin) (Edwards et al., 2018). A study demonstrated that women appear to have significantly higher levels of faecal bifidobacteria and Bilophila than men (Cross et al., 2018; Haro et al., 2016). The diversity seen in the gut microbiota between the sexes may have a dominant role in defining the sex-specific response to medications or provide the foundation to understanding the pathology of disease.

Although men are subject to higher mortality rates, the prevalence of morbidity is higher in women (Singh-Manoux et al., 2008). The onset of disease has also recently been identified to affect normal gut physiology and function between the sexes which consequently alter drug absorption and bioavailability (Freire et al., 2011). For example, the erratic gastric emptying of levodopa in Parkinson's disease patients can reduce the dissolution time of the tablets in the stomach resulting in delayed and incomplete absorption (Deleu et al., 1991). A study showed that a significantly higher bioavailability of levodopa was found in all female patients with Parkinson's disease (PARKD) where the area under the curve was almost 1.6 times higher than in their male counterparts (Kumagai et al., 2014). The study did not investigate further into why sex differences were found, but hypothesised the potentially negative influence of oestrogen in patients with PARKD. Although the underlying mechanism of PARKD is still unclear, the effects of oestrogen on

PARKD symptoms that are mediated by the modulation of the basal ganglia have been shown to exacerbate classic parkinsonism disorders in human PARKD patients (Van Hartesveldt et al., 1986; McEwen, 2014).

Research invested in to understanding the differences between the sexes in the main site of drug absorption continue to be very limited. It is clear that males and females differently respond to medicines due to the dynamic interplay of GI fluid volumes, luminal pH, transit time, expression of membrane transporters, the microbiome and the onset of disease. As such, drug development is required to invest in specialised sex-specific studies to fully understand the mechanism of the gut and to maximise effective oral drug bioavailability.

3.4. Ethnic and genetic factors

Ethnicity can be considered as an important demographic variable that may contribute to significant interindividual variability in PK and pharmacodynamics of several drugs. Regulatory authorities are expecting a sponsor developing a medicine for a new geographical region to consider how to “deal with the possibility that ethnic factors could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations” (ICH, 1998). Ethnic variation in drug absorption may be attributed to intrinsic factors such as variation in the genetics or physiology, or to extrinsic factors such as socioeconomic background, culture and environment with major differences in the diet (Chen, 2006; ICH, 1998; Johnson, 1997).

When considering passive processes in intestinal absorption, ethnic differences as such are not anticipated (Johnson, 1997). However, with drugs undergoing active transport and metabolism in the gut there is more potential for differences. An example is the active calcium absorption with fractional absorption of calcium in premenarchal girls of African origin being significantly higher compared to Caucasian girls (Johnson, 1997). Apart from CYP3A4, also CYP2C9 and CYP3A5 are considerably expressed along the GI tract (Drozdzik et al., 2018). CYP3A4 is known to have largely variable expression between subjects, but limited information is available comparing the CYP3A4 expression or activity in different ethnic groups. Further, little evidence is available regarding clinically significant polymorphisms in the CYP3A4 gene. However, polymorphism in the CYP3A5 gene can make a significant contribution to the variability in drug absorption in different ethnic groups, particularly for substrates with preferential metabolism by CYP3A5 over CYP3A4, such as tacrolimus (Zanger and Schwab, 2013). The ethnic differences in tacrolimus PK were suggested to be related to intestinal metabolism rather than hepatic elimination, and thus the CYP3A5 genotype can affect absorption profiles of extended-release and immediate-release oral formulations (Chen and Prasad, 2018). The most studied polymorphism is CYP3A5*3, and those with homozygous condition are considered as non-expresser. This polymorphism is less frequent in populations of African origin as compared to Caucasians (Chen and Prasad, 2018). Indeed, the prescribing information of orally dosed tacrolimus capsules advice African American patients to receive a higher dose to attain comparable plasma trough concentrations compared to Caucasian patients (FDA, 1994).

For the efflux transporter P-gp, many polymorphisms in the *ABCB1* gene have been associated with altered expression of P-gp, potentially leading to changes in drug PK (Wolking et al., 2015). One of the most common variants, 3435 C>T, shows remarkable interethnic variability, and people of African origin due to their lower allele frequency could be expected to have higher plasma concentrations for P-gp substrates than other ethnic groups, such as East Asians, Indians, and Caucasians. However, the clinical significance remains inconsistent and equivocal (Cascorbi, 2006; Wolking et al., 2015).

In addition to P-gp, BCRP, another efflux transporter expressed in the GI tract, can have a clinically significant effect on drug absorption. For the gene coding for BCRP, *ABCG2*, a much studied single nucleotide polymorphism, Q141K (421C>A), has been shown to decrease BCRP

expression and activity, and this polymorphism has a highly variable frequency depending on ethnicity (Heyes et al., 2018). It is common in Asian populations, where about one third of Japanese and Chinese subjects are affected, while more rare in Caucasian, Sub-Saharan, or African American populations (Heyes et al., 2018). As BCRP is expressed in many tissues, including the intestine, it is complicated to interpret the role of the transporter on the PK. Examples where altered PK is considered to be due to tissue-specific BCRP interaction is atorvastatin and rosuvastatin, where a change in absorption parameters has been observed, but no effect on the elimination half-life (Heyes et al., 2018; Li and Barton, 2018). The FDA label of rosuvastatin states “PK studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls” (FDA, 2003c). Consequently, a lower rosuvastatin dose is suggested for Asian subjects. What complicates the assessment of the precise mechanism for this ethnic difference is that not only the polymorphism of *ABCG2*, but also that of *SLCO1B1*, a gene coding a hepatic transporter OATP1B1, can have an effect on rosuvastatin PK (Li and Barton, 2018; Wu et al., 2017).

Even though there is limited evidence for clinically meaningful ethnic disparities in gastric pH, emptying, intestinal motility, transit time or mucus properties, ethnicity may be associated to these properties through extrinsic factors such as the diet. For example, some ethnic groups may have more vegetarians than others. Vegetarians, compared with non-vegetarians, are expected to have more rapid GI transit time, thus impacting the residence time of the dosage form in the intestine (Chen, 2006). However, ethnic differences in gastric pH can exist as lower gastric acidity has been found in the Japanese population (Tamboli et al., 2010). Implications of specific pharmaceutical product designs on the PK of drugs prescribed for various ethnic groups and genetic variants need to be considered, especially for the drugs that exhibit active processes in absorption and have narrow therapeutic index. More mechanistic studies are needed for detailing the contribution of various factors. Especially, the interrelationship between P-gp and CYP3A, with a highly variable interindividual expression, and potential food-drug interactions, makes it difficult to elucidate the precise ethnic differences in drug absorption.

3.5. Diet

The interaction between food ingestion and drug absorption is well described in several recent review papers (Deng et al., 2017; Mouly et al., 2017; Peter et al., 2017; Van Orten-Luiten, 2017; Witkamp and van Norren, 2018). The postprandial effect of food intake in the GI tract is complex and includes increased viscosity of luminal contents, delay in gastric emptying, elevation of gastric pH, enhancement of splanchnic blood flow and stimulation of bile secretion (Deng et al., 2017). The interaction between food components and drugs mainly takes place in the GI tract before absorption and thus can affect the PK profile of the drug. The effect on a specific drug is dependent of the physico-chemical characteristics of the drug and also the nature of the food. For lipophilic drugs, a positive food effect, i.e., increased absorption upon ingestion of, especially, a high-fat meal, is most prevalent (Deng et al., 2017). Postprandially, the ingested food will react directly or indirectly with drugs through changes in the GI tract. Deng and colleagues made a distinction between different food categories, drug categories and dosage regimens; within the food categories (i.e., different composition of food) a distinction is made between high-fat, high-protein, high-fibre, metal-rich, purine-rich and high-carbohydrate food (Deng et al., 2017). The high-fat diet, which is reflected in the U.S. FDA test meal (FDA, 2002) delays gastric emptying, induces bile secretion, stimulates the intestinal lymphatic transport pathway, inhibits epithelial efflux transporters and may induce diarrhoea. A high-protein diet (although not clearly defined) can inhibit intestinal amino/peptide transporters, stimulate intestinal transporter systems and hepatic enzyme activity. A high-fibre meal is recognised for

its postprandial adsorption of bile acids and stimulation of fermentation in the gut lumen, influencing the gut microbiota. High-carbohydrate food, like high-fat meals, retards the gastric emptying. Thus, Deng and colleagues conclude that one food item or a specific diet can interact through different mechanisms, thus having diverse effect on different drugs (Deng et al., 2017).

Food components can also impact drug absorption via metabolising enzymes and transporters (Won et al., 2012). The most well-known specific interaction here is the inhibition of intestinal CYP3A expression and activity by grapefruit juice (Mouly et al., 2017). Similar interaction is assumed with P-gp transporters, which were shown to be inhibited by citrus juices in vitro (Soldner et al., 1999), but the in vivo relevance has not been fully demonstrated (Becquemont et al., 2001).

Moreover, the gut microbiome and postprandially produced metabolites can affect the absorption of nutrients and pharmaceutical compounds. (Zimmermann et al., 2019) describe that the gut microbiota can modify drug absorption and drugs biotransformation and suggest to take the role of the gut microbiota into account when considering bioavailability and efficacy of drugs. The gut microbiota does not only modify drug absorption, but can be a therapeutic target as well. Food components and diet influence the composition of the gut microbiota and therefore will interact with drug absorption (Falony et al., 2019). Nevertheless, the clinical relevance of all these interactions could be questioned and are often not clear and unexpected interactions could occur (Witkamp and van Norren, 2018).

3.6. Obesity

The prevalence of obesity is increasing and it is now estimated that more than six million adults in Europe are obese (Webber et al., 2014). Obesity is associated with co-morbidities that include type 2 diabetes mellitus (T2DM), ischaemic heart disease, cancer, depression and hypertension, all of which require therapy (Brandt, 2013). Previous work exploring the impact of obesity on drug PK have focused on distribution, metabolism, and elimination aspects rather than absorption (Hanley et al., 2010; Smit et al., 2018). There have also been reviews describing the impact of GI surgery as a treatment for obesity, for example bariatric surgery and Roux-en-Y gastric bypass (Santamaría et al., 2018). Obesity is associated with GI complications which are further described in a recent review (Camilleri et al., 2017).

Obesity has been reported to increase the prevalence of oesophageal disorders; there is a documented link between gastroesophageal reflux disease and obesity in adults, which is likely due to the increased pressure on the stomach and oesophagus due to excess weight (Zacchi et al., 1991). Abdominal obesity has been linked to increased intra-abdominal pressure in subjects whose body mass index (BMI) had a mean value of $49 \pm 10 \text{ kg/m}^2$. However, in an alternative study there was only a weak positive correlation between intragastric pressure and both BMI and waist circumference (El-Serag et al., 2006); (Varela et al., 2009).

The maximum gastric capacity was compared in normal (BMI = $23.6 \pm 2.0 \text{ kg/m}^2$) and obese women (BMI = $40.3 \pm 6.8 \text{ kg/m}^2$). Although the total volumes for each subject group was not reported, the statistical analysis demonstrated no significant differences between the two groups (Geliebter and Hashim, 2001). Two further studies compared gastric volume in lean and obese participants: values in lean and obese were $26 \pm 8 \text{ mL}$ in lean compared to $26 \pm 13 \text{ mL}$ in obese reported by (Juvin et al., 2001) showing no statistically significant difference. In contrast, a study that investigated risk factors for aspiration during anaesthesia compared the gastric volume and pH in lean patients (BMI $18\text{--}25 \text{ kg/m}^2$) versus obese patients (BMI $\geq 35 \text{ kg/m}^2$) and reported larger gastric volumes in the obese ($26.9 \pm 14.6 \text{ mL}$) compared to lean ($6.3 \pm 7.4 \text{ mL}$) (Mahajan et al., 2015). Those studies reporting gastric volumes also reported gastric pH with values of 2.8 and 4.3 in lean participants and values of 2.3 and 3.5 in obese participants by Juvin et al. (2001) and Mahajan et al. (2015),

respectively.

The impact of obesity on gastric emptying is complex with some studies showing no difference (Buchholz et al., 2013; Zahorska-Markiewicz et al., 1986), some showing slower (Jackson et al., 2004) and others showing faster gastric emptying in obese subjects (BMI = $45.3\text{--}58.0 \text{ kg/m}^2$) compared to controls (BMI = $20.3\text{--}24.8 \text{ kg/m}^2$) (Tosetti et al., 1996).

Intestinal transit has been measured in obese (BMI = $34.0\text{--}43.6 \text{ kg/m}^2$) and normal-weight subjects (BMI = $20.0\text{--}26.6 \text{ kg/m}^2$) and similar intestinal transit times have been reported (Wisén and Johansson, 1992). However, the same study showed that the obese population absorbed $74 \pm 4\%$ of the total liquid test meal compared to $50 \pm 5\%$ absorbed in the lean control group. This increased energy uptake may be related to the need for energy transfer to the relatively larger organs present in the obese subjects (Wisén and Johansson, 1992).

The total bile acid concentration was comparable between normal weight (mean BMI = 23.2 kg/m^2) and obese populations (mean BMI = 47.2 kg/m^2) in the fasted state (Diakidou et al., 2009). However, the postprandial concentrations of bile salts were much reduced in obese compared to control populations (Glicksman et al., 2010).

Intestinal transporter expression was investigated in obese compared to non-obese subjects and the following differences were reported: decreased glucose transporter 5 expression (Deal et al., 2018), reduced amino acid nutrient transporter expression (Irving et al., 2016), increased short-chain fatty/monocarboxylate acid transporter expression (Irving et al., 2016), increased levels of CYP1A2 and glucose transporter 4 (Miyachi et al., 2016).

The above differences in GI physiology between normal weight and obese, can indicate potential differences in drug absorption. However, to date there are no reports on the impact of obesity on drug absorption, whereas there are several studies reporting on the distribution and clearance of drugs in obese patients (e.g., Abdussalam et al., 2018; Greenblatt et al., 2018; van Rongen et al., 2018).

3.7. Pregnancy

The effect of pregnancy on drug absorption has been studied using clinical pharmacological tools (i.e., by studying the PK of drugs that are metabolized or transported by a specific enzyme or transporter, and can therefore serve as probe substrates to reflect the activities of the involved enzyme/transporter), as well as via physiological measurements of relevant mechanistic determinants of the absorption process. In terms of gastric acid secretion, several previous reviews report increased gastric pH during pregnancy (Costantine, 2014; Pariente et al., 2016). However, looking back to several original studies, which addressed heartburn during pregnancy, learns that there are also reports of no major changes in gastric pH taking place between the different trimesters of pregnancy and the non-pregnant situation. In these studies also no significant effect of pregnancy on basal and peak acid outputs could be found, suggesting that changes in gastric acidity may not be that prominent (O'Sullivan and Bullingham, 1984; Van Thiel et al., 1977). In terms of gastric emptying, it has been demonstrated using ultrasound studies that gastric emptying time for fluids does not appear to be affected by pregnancy (Chiloiro et al., 2001). In line with this, it was found that the absorption of acetaminophen (maximum plasma concentration (C_{\max}), time to C_{\max} (T_{\max})), was not altered by pregnancy over the trimesters and compared to non-pregnant women (Whitehead et al., 1993). The authors reasoned that due to the very rapid absorption of this drug from the small intestine, gastric emptying will be absorption-limiting. Hence, the fact that no differences occur in absorption profile also led them to conclude that gastric emptying times are not very different between trimesters. Nevertheless, overall GI transit time was found to be longer in the third trimester, indicative of an overall lower intestinal motility (Chiloiro et al., 2001). Consequently, intestinal absorption may be delayed during pregnancy

possibly resulting in slower T_{\max} and lower C_{\max} values for drugs in which the intestinal transit time is the rate-limiting step.

The ultimate bioavailability of drugs is also determined by enteric first pass metabolism, the extent of which can be affected by changes in the expression of drug metabolizing enzymes. The same holds true for compounds that are subject to active transport. The changes in expression of metabolizing enzymes and transporters are in many cases secondary to changes in hormone levels, such as progesterone, oestrogens or cortisol. Substrates of CYP3A4 (e.g., midazolam), CYP2D6 (e.g., fluoxetine), CYP2C9 (e.g., glibenclamide), as well as UGT1A1 (labetalol) and UGT1A4 (lamotrigine), experience increased enzyme activity during pregnancy, which may result in lower bioavailabilities. In contrast, activity of CYP1A2 (caffeine) and CYP2C19 (proguanil) decline during pregnancy, hence an opposite effect may be expected (Fischer et al., 2014; Hebert et al., 2008; Hebert et al., 2009; Heikkinen et al., 2003; Knutti et al., 1981; McGready et al., 2003; Ohman et al., 2008; Wangboonskul et al., 1993). However, as overall oral bioavailability is also determined by hepatic first pass metabolism, it remains difficult to delineate to which extent the changes in PK are the result of changes in enzyme expression occurring in the gut. Although limited direct data is available on the expression of drug metabolising enzymes and transporters in the intestine during pregnancy, changes in activity may be derived from clinical PK studies that have investigated drug disposition after oral administration during pregnancy and the non-pregnant situation (Broe et al., 2014; Deligiannidis et al., 2014; Leke et al., 2018; van der Galiën et al., 2019). Quantitative proteomic analysis of the expression levels of transporter

and different CYP and uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes in the intestine of pregnant women will help to address this question further (Groer et al., 2014; Miyauchi et al., 2016).

An improved understanding of quantitative changes in the expression levels of enzymes and drug transporters or the availability of useful probe substrates or endogenous markers that reflect enzyme and transporter activity would further improve our understanding of the impact of pregnancy on drug absorption. At the same time, this type of mechanistic information is useful to build better *in silico* PBPK models for prediction of oral absorption and bioavailability in this specific patient population, as reviewed in Section 6 of this paper and by others (Abduljalil et al., 2012; Ke et al., 2018).

4. Diseases in the GI tract

4.1. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is an umbrella term for inflammatory conditions that affect the GI tract, mainly the small intestine and the colon. The aetiology of IBD is not fully understood (Bilsborough et al., 2016). IBD includes two major inflammatory conditions of unknown aetiology, Crohn's disease (CD) and ulcerative colitis (UC). Both are associated with a variety of intestinal and extra-intestinal features. Extra-intestinal manifestations are usually related to intestinal disease activity and may precede or develop concurrently. However, the GI areas that are affected can be quite different in CD and UC (Hendrickson et al., 2002).

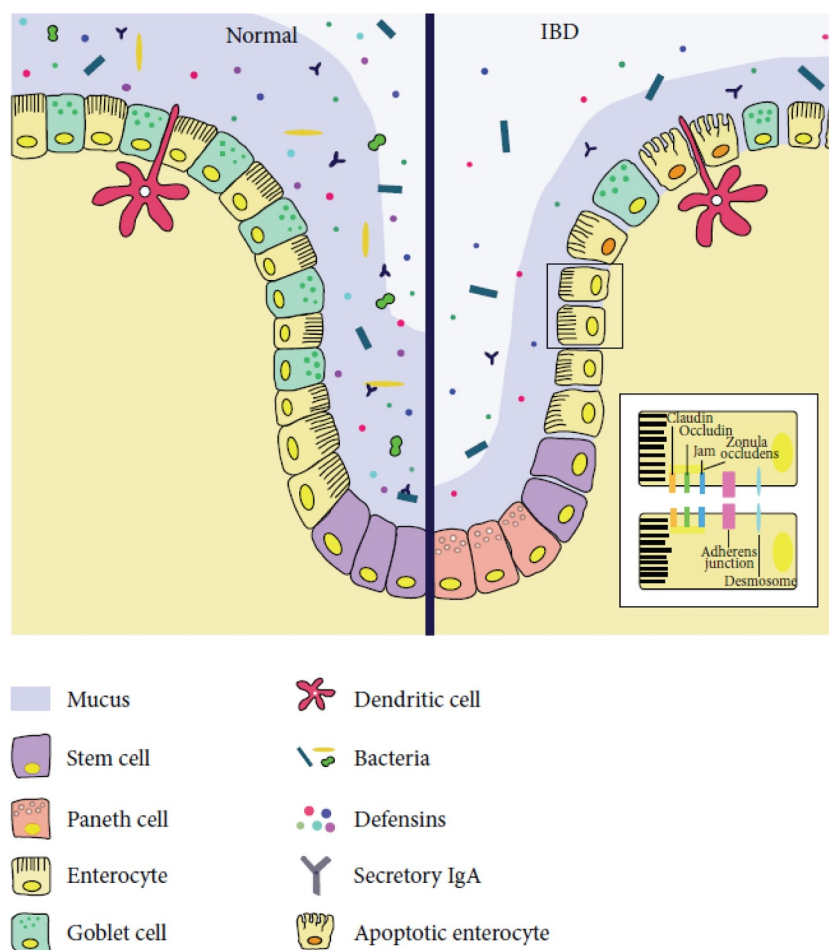


Fig. 1. Components of the mucosal barrier in healthy gut (left) and inflammatory bowel disease (IBD) (right). For detailed explanation, please refer to (Michielan and D'Inca, 2015). The basic structure of tight junctions and other junctional complexes are shown in the bottom-right box. JAM: junctional adhesion (copied from (Michielan and D'Inca, 2015) with permission).

Numerous review and research articles on the pathology, clinical presentation and treatment of CD and UC can be found in the literature. The major treatment goals of current therapies are to decrease the inflammatory reaction, minimize symptoms, improve quality of life, and minimize progression and complications of disease (Sairenji et al., 2017). Even though in many patients it is possible to induce and maintain phases of remission, in both diseases, chronic inflammatory changes of the intestinal epithelium dominate epithelial histology.

CD is a chronic transmural inflammation, i.e., it can affect the entire thickness of the bowel wall, and also any segment of the GI tract from mouth to anus. The inflammation pattern is usually discontinuous with inflamed segments and so called “skip areas” of healthy tissue. The initial location of CD is most commonly in the distal ileum and the earliest mucosal lesions often appear over Peyer's patches (Xavier and Podolsky, 2007). Approximately half of the patients suffer from inflammations that are localized in the distal ileum and proximal colon. The inflammatory reaction can also appear in the proximal parts of the small intestine and/or the colon and, in some patients, also the upper GI tract can be involved. Inflammation can decrease the functional surface area of the intestines, but results from various studies indicate that it also can increase intestinal tight junction permeability (Michielan and D'Incà, 2015). Increasing the pore size of intestinal tight junctions contributes to an increased tight junction permeation of larger molecules, but also bacteria. According to Michielan and D'Incà, CD patients display several defects in the many specialized components of mucosal barrier that regulate paracellular permeability (Michielan and D'Incà, 2015). A schematic comparison of the components of the mucosal barrier in the gut of a healthy subject and an IBD patient is given in Fig. 1 (Michielan and D'Incà, 2015).

UC shows a continuous distribution in the intestinal mucosa and is generally confined to the colon (Stein et al., 1999). It includes diffuse mucosal inflammation that extends proximally from the rectum to a varying degree (Xavier and Podolsky, 2007). Occasionally, it extends into the terminal ileum (Haskell et al., 2005). Histologically, UC involves the innermost lining of the colon. In conjunction with severe inflammation, an extensive superficial mucosal ulceration can be observed (Xavier and Podolsky, 2007). Due to the presence of a significant number of neutrophils within the lamina propria and the crypts, micro-abscesses are formed and another common feature is the depletion of goblet cell mucin (Xavier and Podolsky, 2007). Even though the inflammation is mainly restricted to the colon, there is evidence for some functional small intestinal abnormalities as well. Mourad et al. reported that small intestinal dysfunction is a common feature in UC patients (Mourad et al., 2017). With the intention of better understanding the impairment of small intestinal function in UC, they screened the relevant literature for case studies focusing on intestinal dysfunction in UC and summarized that even though the pathophysiology of the dysfunction has not been elucidated, there is evidence for a decrease in fluid, electrolyte, amino acid, fat, and carbohydrate absorption, as well as for a deranged intestinal motility (Xavier and Podolsky, 2007).

Oral drug absorption in IBD patients is altered due to impaired mucosal barrier function. The type, pattern and severity of the disease is likely to determine whether the reduced total absorptive surface area, or the increased tight junction permeability, also referred to as “leaky-gut-syndrome”, will be the major determinant of the plasma profile of orally administered drugs. However, gut wall permeability is only one factor to consider when discussing oral drug exposure. GI parameters that affect rate, timing and site of *in vivo* drug release are of equal importance. Surprisingly, even though numerous articles and guidelines have been published on various aspects of diagnosing and treating IBD, a systematic review of how IBD affects GI parameters relevant to oral drug exposure is not available.

One of the major GI symptoms in both CD and UC is diarrhoea. Patients often present with severe and chronic diarrhoea. Consequently, GI transit in these patients can significantly differ from that in healthy patients. However, in CD patients, constipation is also a common

symptom. It results from a so-called stricture resulting from thickening of the intestinal wall. Stricture involves narrowing of a small intestinal section and in the worst case can block the flow of digestive contents. GI transit of the luminal contents and dosage forms in IBD patients can thus be significantly different from healthy subjects.

In the recent past, several review and research articles on GI motility in IBD patients have been published. Bassotti et al. reviewed results from studies focusing on colonic motility in UC patients and summarized that UC patients present colonic motor abnormalities, including a lack of contractility and an increase in propulsive contractile waves (Bassotti et al., 2014). Yung et al. assessed GI pH, transit, and motility in 12 patients with known or suspected CD using a wireless-motility capsule (Yung et al., 2016). The motility index in stomach, SI and colon was significantly lower in patients with CD. Since this was the very first study with a wireless-motility capsule in CD patients, at this stage, these observations can only indicate a potential trend, but with the wireless-motility capsule technology, it should be possible to gain a much better insight into GI motility and transit in IBD patients in the near future.

Nugent et al. reviewed the literature with regard to intestinal luminal pH in IBD and concluded that some data indicate that colonic pH is reduced in UC patients, particularly in active disease (Nugent et al., 2001). They could not draw a definite conclusion on intraluminal pH in CD patients, but overall, pH conditions reported in the articles reviewed by Nugent et al. were quite similar to those in healthy controls.

There is currently next to no information available on small intestinal fluid properties and composition in IBD patients (Barkas et al., 2013). A bit more information is already available on colonic fluid properties. With the aim of characterizing the fluid composition in the ascending colon of fasted UC patients in relapse and in remission, Vertzoni et al. analysed the properties of ascending colonic fluid of twelve UC patients (Vertzoni et al., 2010). Of potential relevance for drug absorption, the pH was lower and the buffer capacity higher in IBD patients compared with healthy subjects. More recently, Müllertz et al. presented results from a study on assessing ascending colonic fluid composition, which indicate the presence and structure of some remnants of lipolytic products in the ascending colon of UC patients (Müllertz et al., 2013). However, as for the small intestine, there are still a lot of knowledge gaps to be filled and the same is true for gastric conditions.

In summary, it is obvious that IBD can affect oral drug absorption significantly, but there is a need to fill several essential knowledge gaps. When designing experiments for assessing essential GI parameters, the large inter- and intraindividual variability in pattern and severity of the inflammation in both CD and UC will require particular attention. Moreover, the increasing number of paediatric and adolescent patients, in whom IBD is often following a more complicated and aggressive course than in adult onset (Grover et al., 2017; Rosen et al., 2015), should be properly addressed.

4.2. Cancer in the GI tract

The GLOBOCAN statistic report for 2018 predicted a total of 18.1 millions newly diagnosed cases of cancer, together with expected 9.6 millions cancer-related deaths worldwide (Bray et al., 2018). Out of those numbers, colorectal cancer and gastric cancer rank third (10.2%) and fifth (5.7%) in total cancer incidence, respectively, while they are positioned as second (9.2%) and third (8.2%) cause of death among cancer patients (with pancreatic cancer causing 4.5% of deaths globally).

Primary treatments for GI cancer include surgical removal of the tumor tissue, chemotherapy, radiotherapy and targeted therapy (Gulbake et al., 2016; Orditura et al., 2014). Usual intravenous administration of chemotherapeutics causes various side effects like nausea, vomiting, neutropenia, hematological disorders, and general fatigue (Lin et al., 2015) due to unspecific activity of drugs on both cancer and healthy cells. In order to avoid these effects, targeted

delivery of drugs to the GI tract could offer a much-needed replacement, also with the convenience of patients in mind (Amidon et al., 2015; Banerjee et al., 2017; Derakhshankhah et al., 2017). Well-designed oral chemotherapy can result in low plasma drug concentrations, and concomitantly achieve a prolonged drug exposure to the cancerous cells in the GI tract, resulting in better efficacy and fewer side effects than an intermittent parenteral chemotherapy (Joshi et al., 2014).

Gastric cancer causes changes in physiological function of the stomach manifested as delayed gastric emptying. While delayed gastric emptying has been reported as one of the features of gastric cancer (Tatsuta et al., 1990), it is also one of the most common postoperative syndromes of (partial) gastrectomy, which is a treatment for gastric cancer. As reported in several studies (Kim et al., 2017; Pradhan et al., 2017) delayed gastric emptying develops in 7% to 52% of patients that underwent distal gastrectomy, with this time declining in the post-operative period. However, a study by Chang et al. including 28 patients with non-obstructive gastric cancer, showed no difference in water gastric emptying time compared to control group (15.51 \pm 2.21 and 16.82 \pm 2.13 min, respectively) (Chang et al., 2004). Delayed gastric emptying represents burden for the patients, but also an important fact for the physicians in determining the medication dosage.

The gastric pH has been found to be as high as pH 6–7 in gastric cancer patients (n = 89) (Lu et al., 2010). This increase in the pH of gastric juices is explained by gastric atrophy, which results in reduction of parietal cell mass and cause reduction or absence of detectable gastric acid (Ghosh et al., 2011). Human gastric cancer cell lines were found to have an increased expression of membrane transporters belonging to ABC and the family of efflux proteins, such as multidrug-resistance-associated protein 1 (Obuchi et al., 2013). Inhibition of these and other efflux carriers (e.g., reduced folate carrier 1, multidrug-resistance-associated protein 5, monocarboxylate transporter 4) represents an option to increase cancer cell susceptibility to locally acting cancer drugs (Lee et al., 2016). Other potential targets of drug action, besides efflux transporters, are proposed in reviews by Yu and Xie (2016) and Kang et al. (2004). Drug absorption studies with gastric cancer tissue is highly recommended to assess the drug absorption characteristics of a therapeutic compound as performed by Hultman et al. (2014).

Drug absorption changes in cancer types affecting other GI segments and accessory organs of digestion, such as aggressive pancreatic cancer, hepatic cancer or the very rare small intestine carcinoma, remain poorly studied. In the case of pancreatic cancer, the altered function of the gland leads to decreased exocrine secretions, changes in intraluminal pH, motility disorders and bacterial overgrowth in the intestine (Feig et al., 2012; Ma et al., 2019; Olesen et al., 2013). These effects directly influence drug absorption from the GI tract, especially in the case of lipophilic drugs whose dissolution is decreased with lowered exocrine function of pancreas. Drug resistance is also seen in pancreatic cancer, most likely related to the increased expression of monocarboxylate transporter 4 and solute carrier 1A5 (Grasso et al., 2017). Further research is needed to understand the mechanism of drug sensitivity and resistance through ABC carriers in pancreatic carcinoma as proposed by Adamska and Falasca (2018). Pathological changes in small intestinal tissue can potentially affect the absorption process, but since typically only a small area of the total small intestinal surface is affected, the impact on the overall absorption is limited.

As mentioned above, colon transit time in the general population is characterized by large inter-individual differences (Becker et al., 2014; Sarosiek et al., 2010). Unfortunately, no data on colorectal cancer effect on colon transit time could be found. Although bowel motility changes have been widely accepted as one of the signs of colon cancer, findings from the epidemiological studies are giving inconsistent results (Park et al., 2009; Simons et al., 2010). No effect on the transit time through the upper GI tract was noticed after colorectal resection as therapy of colon cancer (Matsuoka et al., 2011). As with the colon transit time, previous studies have shown no differences in intraluminal

pH at patients diagnosed with colorectal cancer (McDougall et al., 1993; Pye et al., 1990). Further analysis in terms total colonic fluid volume and composition in colorectal cancer patients are required since very scarce data are available for these properties, which will affect drug transit and absorption.

Colorectal cancer starts with epithelial changes in the colon by formation of adenomatous polyps (Simon, 2016), which can affect the absorption process through the colonic epithelium. The absorption of some drugs depends on membrane transporters, which are present to a greater extent on the surface of colonic epithelial cells compared to other parts of the GI tract (Calcagno et al., 2006). The expression of membrane transporters in the GI tract is influenced by pathophysiological processes such as cancer. Various studies have identified modified expression of membrane transporters in intestinal cancer cells, in particular for members of the ABC or solute carrier group of proteins (Cui et al., 2017; Devriese et al., 2017; Lozoya-Agullo et al., 2015; Pinheiro et al., 2008; Trumpi et al., 2015). Several comprehensive recent reviews on variation of the transporter expression on cancer cell membranes in different stages of the disease, as well as in different colorectal cancer cell lines, are available (Da Silva et al., 2015; Gonçalves and Martel, 2016). For the purpose of testing intestinal drug absorption, model systems such as the Caco-2 cell line (Calcagno et al., 2006; Devriese et al., 2017; Tannergren et al., 2009) and murine cell models (Kim et al., 2012) have been used. Caco-2 cells appear to be more similar to healthy small intestinal tissue than to cancerous colorectal tissue (Calcagno et al., 2006). Thus there is a need for colon cancer cell lines to study the absorption properties of cancer cells. These model systems should preferably be accompanied with tests on *ex vivo* tissue samples, as suggested by Calcagno et al. (2006) and Collett et al. (2008). Increased expression of drug efflux transporters (P-gp, BCRP, multidrug-resistance-associated protein) in colorectal cancer cells (Hu et al., 2016) accompanied with increased glycosylation of the transporters and other molecules on the cancer cell membrane (Very et al., 2018) has been reported. The expression of certain drug transporters also correlates with the progression of the disease (Gotanda et al., 2013; Hlavata et al., 2012). *In vitro* models of drug absorption in cancer have been developed based on the expression of transporters in cancer cells in order to predict the absorption of drugs dosed in combination therapies (Bekusova et al., 2018).

Bekusova et al. found that the paracellular permeability (opening of tight junctions) in colorectal cancer varies depending on the tumour location. The tumour tissues were less permeable than the intact intestinal membrane, while the tumour-adjacent tissues exhibited an increased paracellular permeability (Bekusova et al., 2018). Passive transcellular absorption of drugs is also affected by neoplastic changes of the colonic cells. Changes in the properties of the transcellular transport systems in cancer cells should be considered when designing the new molecular entities intended for treatment of colon cancer.

As presented, cancer pathologies of the GI tract do affect drug absorption through the alteration of the GI tract physiology, in particular the modification or damage of the GI epithelium. These alterations require careful consideration when patients are treated with oral therapeutics to treat the disease itself or associated comorbidities such as diabetes or hypertension.

4.3. Roux-en-Y gastric bypass

The prevalence of obesity is growing (see above), and it is associated with an increased demand for bariatric surgery; especially Roux-en-Y gastric bypass (RYGB, Fig. 2) and sleeve gastrectomy are gaining ground. With a sleeve gastrectomy, there is only a restriction of the size of the stomach by creating a gastric tube (Neff and le Roux, 2014). When performing a RYGB, a small gastric pouch is formed and the proximal part of the small intestine is bypassed. The gastric remnant and bypassed biliary limb is reconnected to the intestine 75 to 150 cm distal to the anastomosis between the gastric pouch and distal part of

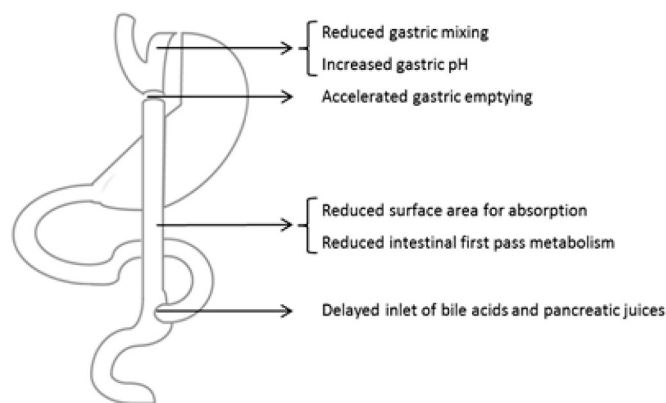


Fig. 2. Schematic representation of Roux-en-Y gastric bypass (RYGB).

the jejunum. These anatomical and physiological changes of the GI tract including changes in volume of the stomach, gastric pH, gastric emptying, inlet of bile acids, surface area for absorption and transit time, can all affect the intestinal drug absorption. This can result in altered drug disposition, namely decreased (Gesquiere et al., 2016), increased (Padwal et al., 2011) or comparable (Gesquiere et al., 2015) bioavailability after RYGB. A good insight into these changes is important as they can result in potentially dangerous over- or under-dosing. In this section, we focus on the changes following RYGB.

Gastric mixing promotes disintegration, which is required for drug absorption. Gastric mixing, and thus disintegration, may be reduced as the stomach volume is reduced after RYGB (Padwal et al., 2010). To avoid the need for disintegration, drugs can be administered as a liquid formulation, crushing/chewing solid formulation or as an orodispersible formulation, if this is available for the drug involved.

A small gastric pouch, which is separated from the native stomach, is created in patients with a gastric bypass. In the study of Smith et al. (patients with RYGB: $n = 10$; controls: $n = 15$), the gastric acid secretion from the gastric pouch was markedly reduced compared to the gastric acid secretion from the total stomach of age- and sex-matched control subjects (Smith et al., 1993). This was the case for both the basal secretion (mean \pm Standard error of the mean: 0.01 ± 0.01 mEq/h post-RYGB vs. 4.97 ± 0.66 mEq/h in the control group) and the pentagastrin-based stimulated secretion (0.08 ± 0.04 mEq/h post-RYGB vs. 12.11 ± 1.34 mEq/h in the control group) (Smith et al., 1993). These findings were confirmed by Behrns et al. (Behrns et al., 1994), indicating that the gastric acid secretion after gastric bypass is negligible as most of the parietal cells (i.e., acid-producing cells) are bypassed. This results in an elevated gastric pH, which will have an impact on the solubility of drugs as it influences the ionization (De Smet et al., 2013). Basic drugs will have a decreased solubility after RYGB as there is less ionization, and acidic drugs will have an increased solubility, as there is more ionization. In modelling studies, an average pH of 6.6 was set to simulate the gastric pouch after RYGB in fasted state (Darwich et al., 2012; Seaman et al., 2005). An *in vitro* analysis of the dissolution of psychiatric medications after RYGB showed that the dissolution of 10 out of 22 drugs was significantly reduced, while two drugs had significantly greater dissolution in a post-RYGB environment in comparison with a control environment (Seaman et al., 2005). The level of dissolution gives no direct information on the therapeutic effect of drugs, but it provides already an indication of the level of absorption since the absorption of drugs is often limited by the dissolution rate.

Gastric content, hormones and neural influences regulate gastric emptying. It has been shown by different methods (e.g., D-xylose test, paracetamol test and scintigraphic measurements) that gastric emptying for liquids is accelerated after RYGB (Dirksen et al., 2013; Horowitz et al., 1982; Morinigo et al., 2006; Näslund and Beckman, 1987; Wang et al., 2012). Oral administration of a liquid drug

may therefore result in faster absorption and in a shorter time to reach C_{max} . The influence of RYGB on gastric emptying for solids is more controversial, as Horowitz et al. have shown that the gastric emptying for solids is slower postoperatively, while Dirksen et al. have shown that it is faster (Dirksen et al., 2013; Horowitz et al., 1982).

RYGB is associated with alterations of the anatomical structure of the upper intestinal tract, which could affect the enterohepatic recirculation of bile acids. The inlet of bile acids and pancreatic juices in the small intestine is delayed, thus the interaction between these compounds and food/drugs is delayed (Neff et al., 2013). These changes have mainly an impact on lipophilic drugs as they depend on bile acids for their dissolution/solubility. Furthermore, lipophilic drugs often undergo enterohepatic recirculation, influencing its steady-state concentration (Padwal et al., 2010). Patti et al. showed that, in individuals who had undergone a RYGB 2–4 years before ($n = 9$), the serum concentration of bile acids was more than twofold higher than in overweight ($n = 10$) or severely obese individuals ($n = 5$) without bariatric surgery (Patti et al., 2009). This was the same for the individual bile salts taurodeoxycholic, glycocholic, glycochenodeoxycholic, and glycodeoxycholic acids. This has been confirmed by Simonen et al. ($n = 30$) (Simonen et al., 2012), who have also shown that the total serum bile acid concentration in fasted state was twofold increased post-RYGB. However, the increased secretion of bile acids may not be sufficient to compensate the delayed inlet as it has been shown that the absorption of fat is reduced after RYGB, as mentioned before (Carswell et al., 2014; Kumar et al., 2011; Odstrcil et al., 2010).

Dirksen et al. have studied the small intestinal transit time after a meal by a scintigraphic technique in 17 patients who had undergone a RYGB more than a year before and in 9 healthy control subjects. They have shown that the small intestinal transit time was longer in patients with RYGB compared to control subjects (Dirksen et al., 2013). This does not entirely correspond with the findings of Morinigo et al., who observed that, by performing a lactulose breath test, the oro-caecal transit time was shorter in RYGB-patients. However, the oro-caecal transit includes pouch emptying and small intestinal transit, so it reflects not only the intestinal transit time (Morinigo et al., 2006). Carswell et al. have also measured the oro-caecal transit time using sulphasalazine. In this study, RYGB had no impact on the oro-caecal transit time (Carswell et al., 2014). Dirksen et al. have also determined the colonic transit time, which was unaltered after RYGB (Dirksen et al., 2013).

By performing a RYGB, a part of the stomach and the proximal small intestine is bypassed resulting in a reduction of the functional GI length (Neff et al., 2013). Moreover, the proximal small intestine has the largest surface area of the GI tract by the presence of villi and microvilli. A bypass of the duodenum and the proximal part of the jejunum results in a large reduction of the surface area for absorption (Miller and Smith, 2006; Spak et al., 2010). This can have an impact on the bioavailability of drugs, especially since most of the orally administered drugs are maximally absorbed in the small intestine (Padwal et al., 2010). Besides, Spak et al. have shown that the appearance of the mucosa of the Roux-limb is altered 6–8 months after the surgery (Spak et al., 2010). They showed that the height of the villi was decreased after RYGB, which also contributes to the reduction of the surface area. However, cell proliferation was increased, which might be a compensatory mechanism for the loss of cells at the tips of the villi.

The influence of drug metabolism and drug efflux may vary over distinct parts of the intestine (Padwal et al., 2010). The expression of P-gp increases from the proximal to the distal small intestine, while the expression of CYP450 enzymes is the highest in the duodenum and jejunum and decreases to more distal sites (Stappaerts et al., 2013). Bypassing parts of the small intestine with a high abundance of CYP450 isoenzymes can therefore lead to alterations in oral drug bioavailability as there will be less metabolism and may thus increase the relative influence of P-gp. The majority of drugs enter into the systemic circulation by passive diffusion from the GI tract, provided that they are non-

ionized. Ionized drugs often require active transport for absorption. However, receptors and transporters are not homogeneously distributed throughout the small intestine; hence, bypassing the proximal part of the small intestine can be associated with bypassing receptors or transporters. This can influence the bioavailability of drugs that need these transporters for absorption (Smith et al., 2011).

4.4. Celiac disease

Celiac disease is an autoimmune disorder occurring in genetically predisposed individuals, in whom the ingestion of gluten, a protein from wheat, barley and rye, leads to an immune reaction in the small intestine. Celiac disease generally affects around 1% of the population worldwide (Lebwohl et al., 2018). The occurrence has increased over the past 50 years, and is higher in some countries, e.g., Finland, than in others, e.g., Germany (Lebwohl et al., 2018; Mustalahti et al., 2010). It is estimated that more than two million Americans with celiac disease are not diagnosed and can be at risk for long-term health complications. Prolonged gluten intake in undiagnosed patients can lead to an increase in the incidence of autoimmune diseases such as T1DM, IBD, autoimmune thyroiditis, and also an increased mortality rate (Ludvigsson et al., 2015; Rubio-Tapia and Murray, 2010). The current treatment of celiac disease is a gluten-free diet, and hereby most symptoms, but not all, can be alleviated (Lebwohl et al., 2018; Rubio-Tapia and Murray, 2010; Samsel and Seneff, 2013).

The classical symptoms of celiac disease include chronic diarrhoea and weight loss, but also symptoms like bloating, constipation, chronic fatigue, headache, abdominal pain, and osteoporosis are prevalent (Downey et al., 2015). Celiac disease is manifested in the small intestine as an increased number of intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy (Lebwohl et al., 2018; Rubio-Tapia and Murray, 2010). Most often, villous atrophy is found in the duodenum, but it can also affect more distal parts of the small intestine. The areas of villous atrophy tends to be patchy and are dispersed between regions of normal mucosa (Ciaccio et al., 2016). Villous atrophy results in a flattening of the microvilli, which in turn gives a decreased absorptive surface area in the intestine, which can impair the ability to absorb nutrients (Ciaccio et al., 2016; Samsel and Seneff, 2013). Accordingly, celiac disease is associated with deficiencies in iron, vitamin D3, molybdenum, selenium, and cobalamin (Samsel and Seneff, 2013). It is therefore possible that intestinal drug absorption will also be negatively affected. However, it is also well accepted that the intestinal permeability is increased, in part due to opening of tight junctions, which can potentially increase drug absorption (Heyman et al., 2012; Kuitunen and Savilahti, 1996; Vilela et al., 2008).

Details on other changes in the small intestine in untreated celiac disease are scarce. A single study has examined the pH on the jejunal surface in untreated patients and compared it with the pH of patients on a gluten-free diet. The study showed a significantly higher pH in untreated celiac disease patients, which also might impact absorption of ionizable drugs (Kitis et al., 1982). Another study by Lang et al. (1996) found that the activity of CYP3A4 was decreased in adult untreated patients, compared to healthy subjects, and Johnson et al. found the same for paediatric celiac disease patients (Johnson et al., 2001). This is likely to be related to the villus atrophy, as the CYP enzymes are primarily located in the apex of the enterocytes, in a band just below the microvillar border (Lang et al., 1996). This decrease in CYP3A4 is normalized when patients where on a gluten-free diet (Lang et al., 1996; Samsel and Seneff, 2013).

Celiac disease is associated with delayed gall bladder emptying and decreased pancreatic secretions (Benini et al., 2012). The fasting gall bladder volume and the post prandial residual volume are significantly higher in celiac disease patients compared to controls. These symptoms are reversible and disappear when celiac disease patients get on a gluten free diet. Unfortunately, the intestinal bile salt concentrations have not been determined in any of these patient groups (Benini et al.,

2012; Usai-Satta et al., 2018).

In general, the mouth-to-caecum transit time has been reported to be slower in untreated celiac disease patients, compared to healthy controls, but the literature does not agree as to whether this is normalized when patients are on a gluten-free diet (Benini et al., 2012; Chiarioni et al., 1997). The gastric emptying time is prolonged in untreated celiac disease patients, but is normalized upon intake of a gluten-free diet (Benini et al., 2012; Elli and Bardella, 2005; Perri et al., 2000). In addition, the transit time of a meal through the small intestine is delayed in celiac disease patients, probably due to functional alteration of small intestinal motility, whereas there are no changes in the colonic transit time (Benini et al., 2012; Usai-Satta et al., 2018). An abnormal gastrointestinal motor activity, indicating a neuropathic disorder, in untreated celiac disease patients has been observed and this is persisting in most adult celiac disease patients also during a gluten free diet (Bassotti et al., 2008; Benini et al., 2012). The mechanism involved in this remains unclear, but there might be a low-grade mucosal inflammation even on a gluten-free diet. This in turn has recently been connected to an intestinal sensorimotor dysfunction (Usai-Satta et al., 2018).

The microbiota in celiac disease patients has been shown to be altered, as compared to healthy subjects. Often reduced levels of the commensal bacteria *Enterococcus*, *Bifidobacteria* and *Lactobacillus* are found, together with an overgrowth of pathogenic gram-negative bacteria (Di Cagno et al., 2011; Sanz et al., 2011). A gluten-free diet will change the microbiome, but this is also the case in healthy individuals.

Drug absorption studies in treated and untreated celiac disease patients mostly date back to the 70ties and 80ties and all involve a rather low number of patients (up to 14), and often lack proper controls. In these studies, many drugs showed a higher absorption in celiac disease patients, as compared to control subjects (propranolol, cephalixin, clindamycin, sulfamethoxazole, trimethoprim and methyldopa), whereas paracetamol and practionol displayed a lower absorption (Tran et al., 2013). Thus, a conclusion on the impact of celiac disease on drug absorption cannot be drawn on this point. However, the physiological changes described above make it possible that drug absorption is altered, but more clinical studies in untreated celiac disease patients are needed.

4.5. Lactose intolerance

Lactose intolerance is the consequence of decreased or absent lactase activity in the brush border of the small intestinal epithelium resulting in malabsorption of lactose in the small intestine and fermentation of it in the large intestine. The primary effect concerning drug absorption is related to the osmotic effect of the non-absorbed lactose that also results in diarrheal symptoms. The prevalence of lactase deficiency has been described in most regions of the world and in people with diverse ethnic backgrounds. However, the prevalence of lactose malabsorption and lactose intolerance is unclear due to methodological limitations. The lowest prevalence was seen in Europeans and European Americans and higher prevalence in African Americans, Hispanics, Asians, Asian Americans, and Native Americans (Suchy et al., 2010). Particularly, Asian populations present higher prevalence of lactose intolerance, which originates from the high prevalence of lactase deficiency in these populations (Goh et al., 2018).

The effect of lactose intolerance has most extensively been investigated in patients undergoing thyroid hormone replacement therapy. Lactose intolerance can cause malabsorption of levothyroxine: eliminating lactose from the diet leads to decreased values of thyroid-stimulating hormone in the serum of patients with both Hashimoto thyroiditis and lactose intolerance, indicating less effective absorption of the drug (Asik et al., 2014; Cellini et al., 2014; Munoz-Torres et al., 2006). Therefore, in patients resistant to levothyroxine therapy, lactose intolerance should be considered as a cause. The most recent advance concerning levothyroxine therapy is the development of a novel oral

liquid preparation that has been shown to overcome different malabsorption conditions (Fallahi et al., 2017).

Another study investigated the absorption of isoflavones, which have preventive effects against loss of bone mass and cardiovascular diseases. Serum isoflavone metabolites were measured in participants with and without evidence for lactose malabsorption. Interestingly, the lower absorption of isoflavone glucosides induced by low lactase activity was compensated by bacterial deglycosylation in the large intestine in humans. Therefore, the effect of lactose intolerance on drug absorption depends on the chemical properties of the drug in question, as well as the extent to which the colon participates in drug assimilation processes (Tamura et al., 2008).

4.6. Infectious diseases of the gastrointestinal tract

GI tract infections include acute and chronic disorders of the digestive apparatus induced by viruses, bacteria, and parasites. Most GI tract infections are self-limiting and exhibit acute symptoms lasting 5 to 7 days. However, in some cases the symptoms can persist over a longer period of time and result in a prolonged, persistent, or even chronic disease state. Typical symptoms comprise diarrhoea, nausea, vomiting, abdominal cramping, fever, and/or dysentery. Nausea is typically associated with an increased stomach emptying time. In case of diarrhoea the intestinal motility is often increased which results in a shorter intestinal transit time (Higgs et al., 1975; Spiller, 2006). The overall stool volume is increased and the viscosity of intestinal contents decreased compared to a healthy gut (Schiller, 1999). Finally, GI tract infections can also result in the damage of the intestinal membrane barrier (Barnes and Townley, 1973; Ford et al., 1985) and are often linked to the disruption of the intestinal microbiota system (Aebischer et al., 2006; Kuehl et al., 2005; Sekirov and Finlay, 2009).

The impact of the pathophysiology of GI tract infections on oral drug absorption largely depends on the type, severity, and duration of symptoms. The increased stomach emptying time, associated with nausea and vomiting, delays the onset of action of medications and may result in uncontrolled or sub-therapeutic plasma concentrations. The selection of appropriate dosage forms, such as sublingual or orally disintegrating tablets, suppositories, or parenteral formulations is therefore particularly important in the treatment of patients exhibiting nausea or concomitant diseases.

The decrease in intestinal transit time can significantly affect the absorption of drugs exhibiting an absorption window or pre-systemic metabolism as observed with tacrolimus and cyclosporine. Tacrolimus is rapidly absorbed in the duodenum and jejunum. The absorption is limited by the efflux-transporter P-gp, and tacrolimus undergoes extensive pre-systemic metabolism by CYP3A4 in the gut wall, which both reduce the oral bioavailability to approximately 20%. In gastroenteritis patients, P-gp-mediated efflux and pre-systemic metabolism are reduced due to impaired enterocytes. This results in significantly higher tacrolimus trough levels (Eades et al., 2000; Hochleitner et al., 2001). The opposite effect is observed with cyclosporine A. Cyclosporine A is subject to an absorption window in the small intestine, and the residence time in this segment was shown to be an important determinant of oral cyclosporine exposure (Drewe et al., 1992). In gastroenteritis patients, the increased GI motility and reduced residence time in the gut was shown to significantly reduce the oral cyclosporine exposure.

The impact of membrane damage on oral exposure is difficult to predict and can result in either an increase or a decrease in drug absorption. The loss in mucosal integrity results in an increased permeation of compounds, while villous shortening reduces the absorptive surface area and thus may reduce the total absorption of compounds (Ford et al., 1985). This severe condition directly influences the absorption of oral compounds exhibiting permeability-limited exposure or which are intended for local activity, such as vancomycin (Oami et al., 2017). Such damage typically occurs in case of prolonged symptoms or massive diarrhoea, and therefore, it must be kept in mind that a specific

drug may show different absorption behaviour depending on the length and severity of the GI tract infection (Bolme and Margareta, 1975; Nelson John et al., 1972). Little is known about the impact of GI tract infections on the expression and activity of membrane transporters. The intestinal gut membrane typically regenerates within 2-4 weeks and the absorption of oral compounds may still be altered after the recovery from clinically evident GI tract symptoms.

The microbial imbalance occurring during GI tract infections is critical for drugs that are activated or inactivated by the intestinal microbiome (Li et al., 2016), as reported for several compounds including immunosuppressant, antineoplastic, and cardiovascular medicines (Enright et al., 2016). The impact of the intestinal microbiota system on oral drug absorption is particularly critical for low solubility and/or low permeability compounds, as well as for extended release formulations, which are subject to long residence time in the gut and may therefore interact with the intestinal microbiome.

The impact of infectious GI tract diseases on oral drug absorption is very variable and difficult to predict a priori. It does not only depend on the type, severity, and duration of GI symptoms, but also the specific biopharmaceutical properties of the compound and its dosage form. In the absence of predictive biopharmaceutical methods simulating such altered GI tract conditions, a good mechanistic understanding of the absorption behaviour of the drug (e.g., absorption window, permeability- vs. solubility-limited absorption etc.) is key for estimating the impact of GI tract infections on oral exposure. Attention must be directed towards medicines with a narrow therapeutic index, for which careful plasma concentration monitoring should be considered to ensure safety and efficacy.

4.7. *Helicobacter pylori* infection

Helicobacter pylori (*H. pylori*) is a highly prevalent pathogen causing a chronic inflammation of the gastric mucosa. The clinical outcome ranges from an asymptomatic gastritis to serious conditions such as peptic ulcer or gastric cancer.

H. pylori infection is known to induce alterations in some physiological functions of the stomach, particularly affecting gastric acid secretion and GI motility. The impact on gastric acidity depends on the severity of the infection and distribution of the affected tissue in the stomach. Inflammation in the antral region is associated with increased production of gastrin, which in turn increases acid secretion in the gastric corpus. However, if the corpus is affected by severe inflammation, the response to gastrin is greatly reduced, resulting in reduced capacity to secrete acid (El-Omar, 2006). Thus, *H. pylori* positive subjects can exhibit either increased or decreased stomach acidity. Between 25 and 40% of patients also exhibit antral hypomotility and a delayed gastric emptying (Mearin et al., 1995; Miyaji et al., 1999; Thor et al., 1996). Furthermore, there is increasing evidence that *H. pylori* infection affects the GI functions indirectly by influencing the brain-gut axis (Budzynski and Klopocka, 2014). This may have an impact on the pathophysiology of other organs than the stomach, and generate disturbances in permeability, motility and secretion along the entire GI tract (Budzynski and Klopocka, 2014; Gerards et al., 2001; Su et al., 2000).

The physiological changes induced by *H. pylori* infection can have a significant impact on the drug absorption process and thus important clinical implications as highlighted in several systematic reviews (Fiorini et al., 2015; Lahner et al., 2009; Lahner et al., 2014). Particularly, oral compounds and formulations with pH-dependent solubility need careful evaluation when administered to *H. pylori* positive patients, as observed with thyroxine (Centanni et al., 2006), L-dopa (Pierantozzi et al., 2006; Pierantozzi et al., 2001), and delaviridin (Shelton et al., 2000; Shelton et al., 2003). However, more research is needed to capture the pathophysiology of *H. pylori* infections, its impact on the function of the entire GI tract, and thus, the clinical implications on oral drug absorption.

5. Systemic diseases that change GI conditions

5.1. Parkinson's disease

Parkinson's disease (PARKD) is a progressive neurodegenerative disease that is classically diagnosed after the manifestation of visible motor symptoms such as rigidity, bradykinesia, tremor and postural instability. However, there is a growing body of evidence supporting the hypothesis that non-motor features, especially a variety of GI symptoms could be considered as early biomarkers since they are prevalent among confirmed patients and occur much earlier than the cardinal signs of PARKD, i.e., the motor symptoms (Pfeiffer, 1998; Poirier et al., 2016).

A thorough understanding of the broad spectrum of clinical manifestations of PARKD is essential for a proper diagnosis of the disease. There is evidence that pathological processes that lead to PARKD could be initiated in the enteric nervous system before spreading to the central nervous system. This would be an explanation for the early occurrence of GI symptoms, but to date the pathophysiology of the enteric nervous system component in the aetiology of PARKD is not completely understood (Poirier et al., 2016). According to numerous review articles on GI dysfunctions in PARKD patients published in the recent past, a more detailed picture of the presence and extent of GI dysfunction in PARKD is emerging and over the last decades many abnormalities or disturbances in function at virtually all levels of the GI system have been identified (Fasano et al., 2015; Jost, 2010; Kim and Sung, 2015; Pfeiffer, 2011; Poirier et al., 2016; Su et al., 2017).

A detailed understanding of how and to which extent the GI system is affected in which state of the disease would be essential for developing better oral PARKD medications. It would improve the estimation of how dosing regimens for orally administered drug might be affected by the stage of the disease (Wollmer and Klein, 2017) and the development of appropriate experimental models when the aim is to predict drug release and absorption in PARKD patients using *in vitro* and *in silico* tools.

With the aim of better predicting *in vivo* drug release and absorption of orally administered drugs in PARKD patients, Wollmer and Klein recently reviewed the literature for a reliable set of PARKD-specific GI parameters (Wollmer and Klein, 2017). They found that the level of detail of information available is limited and that reports focus on the discussion of general GI symptoms rather than specific GI parameters.

Typical PARKD-related GI symptoms range from oral issues, including drooling, swallowing problems, nausea, vomiting, early satiety,

bloating and weight loss to constipation which is regarded as one of the most common symptoms (Fasano et al., 2015; Pfeiffer, 2011; Su et al., 2017). These symptoms are, however, just indicators of serious physiological alterations of several GI parameters including a reduced salivary secretion rate and an impaired motility of oesophagus, stomach, and the intestines amongst others. An altered GI environment and transit time may seriously affect PK of orally administered drugs. To date, this issue has been mainly discussed for orally administered PARKD drugs (Fasano et al., 2015; Pfeiffer, 2011), but is of equal importance for all other oral medications taken by a PARKD patient, not only in an advanced stage of the disease, but particularly in early phases, when motor symptoms are not yet developed and the patient is sometimes not even diagnosed with PARKD.

Based on their literature review Wollmer and Klein concluded that even though there is quite a reasonable set of data available on parameters, such as salivary secretion, oropharyngeal and oesophageal passage and gastric emptying, there is still a big lack in knowledge that would be required for addressing all parameters that might be relevant for drug release and absorption during a GI passage in a PARKD patient. The latter is particularly true for contractile motility patterns and pressures in the entire GI tract as well as for the small intestinal transit time. Moreover, it seems that to date next to no attention has been given to potential disease-related changes in GI fluid composition (Wollmer and Klein, 2017). With the availability of novel non-invasive diagnostic options, such as for instance the wireless motility capsule and magnetic resonance imaging and a proper test design, it will hopefully be possible to gather the required information in the near future.

5.2. Cystic fibrosis

Cystic fibrosis (CF) is an autosomal genetic disorder, caused by mutations in the CF transmembrane conductance regulator (CFTR) gene (Gelfond and Borowitz, 2013). World-wide, around 70-80.000 people suffer from CF. In the past, life expectancy for a CF patient was 15-20 years and it was therefore considered a fatal paediatric disease. However, in the last decades life expectancy has increased to 40-50 years, especially in developed countries (Bowen and Hull, 2015; Elborn, 2016). This is partly caused by prophylactic use of oral antibiotics to avoid pulmonary infections (Elborn, 2016).

The CFTR protein is responsible for ion transport across the epithelium, i.e., the lungs and the GI tract, including the pancreatic and hepatobiliary systems (Gelfond and Borowitz, 2013). Mutations in the

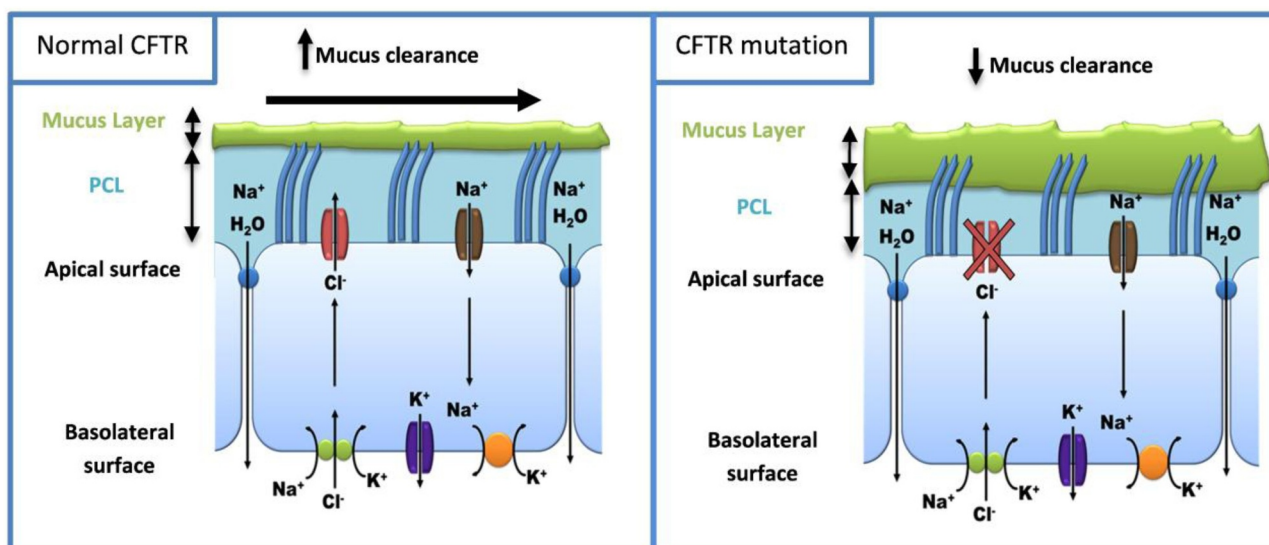


Fig. 3. Schematic illustration of the transporter defects leading to cystic fibrosis (copied from Kumar, 2014 with permission).

CFTR protein results in an abnormal chloride and bicarbonate transport across the apical membrane of the epithelial cells. This in turn leads to the formation of thick, viscous mucus secretions in, e.g., the lungs and the GI tract (Fig. 3) (Bowen and Hull, 2015; Elborn, 2016; Gelfond and Borowitz, 2013). Most CF patients also have pancreatic insufficiency, as well as GI dysmotility disorders, such as gastroesophageal reflux, distal intestinal obstruction syndrome, and chronic constipation (Corral et al., 2016; Gelfond and Borowitz, 2013). Corral and co-workers recently reviewed gastric emptying and incidence of gastroparesis in CF patients. In general, a more rapid gastric emptying was seen in younger patients, whereas the overall CF population had a gastroparesis frequency of 38%, and this was higher for patients >18 years, and especially patients with diabetes (Corral et al., 2016).

The impaired pancreatic and intestinal bicarbonate secretion can lead to a decreased duodenal and jejunal pH, which influences the effect of the enterocoated pancreatic enzyme supplements, taken by CF patients to improve food digestion (Tang et al., 2009). The decreased duodenal and jejunal pH can therefore lead to low and variable absorption of drugs dosed in enterocoated formulations. All in all, the GI symptoms of CF patients often lead to poor nutrient and fat absorption (Duffield, 1996; Elborn, 2016), which in turn could be associated with a reduced absorption of orally dosed drugs, however, this is not clear from the literature. For example, lower and more variable drug absorption for lung transplanted CF patients, compared to non-CF lung transplanted patients has been observed for tacrolimus (Saint-Marcoux et al., 2005), whereas no difference in oral absorption compared to healthy volunteers was found for doxycycline (Beringer et al., 2012). Often studies of oral drug pharmacokinetics in CF patients are carried out without proper control groups (Touw et al., 2000), thus better controlled studies are needed in order to conclude if CF patients in general have impaired drug absorption.

5.3. Diabetes mellitus

Diabetes mellitus is a significant issue with approximately 8.5% of the adult population being affected (Sarwar et al., 2010). There are two main types of diabetes: Type 1 (T1DM), an autoimmune disease, where the body is unable to produce insulin, and Type 2 (T2DM) where insulin secretion is deficient or there is insulin resistance. T2DM is the dominant form in adults and is strongly linked to obesity.

Several authors have recently reviewed gastric emptying in T1DM and T2DM (Chang et al., 2010; Kashyap and Farrugia, 2010; Marathe et al., 2013). Delayed gastric emptying (diabetic gastroparesis) is observed in 30–50% of diabetic patients, with a similar prevalence between T1DM and T2DM. However, in some diabetic subjects, abnormally rapid gastric emptying can also occur (Chang et al., 2010; Marathe et al., 2013). Alterations in plasma glucose levels also have an impact on gastric emptying: severe hyperglycaemia slows gastric emptying of solids and liquids, whereas insulin-induced hypoglycaemia increases the gastric emptying rate, even in subjects with an underlying delay in gastric emptying (Chang et al., 2010). An increase in gastric pH is associated with diabetic gastroparesis (Hasler et al., 2008).

Wegener et al. investigated GI transit in insulin-treated diabetic patients (Wegener et al., 1990). Three aspects of GI transit were studied, i.e., gastric emptying (using scintigraphy), oro-caecal transit time (using a hydrogen breath test), and whole gut transit time (using appearance of indigocarmine in the stool). Both T1DM and T2DM patients were enrolled in the study, which was performed in the fed state. Gastric emptying was significantly delayed in diabetic patients compared to healthy controls. While the difference in median % gastric retention at 60 min was modest (approximately 69% vs. 72% in healthy controls), 35% of diabetic patients had a % retention at 60 min that was higher than the upper limit of the normal range. For oro-caecal and whole gut transit time, there was no significant overall increase in the diabetic group, although the proportion of subjects with prolonged oro-caecal transit time (>135 min) or prolonged whole gut transit time

(>29 h) was higher in the diabetic group than in the control group (23.0% vs. 3.6% for oro-caecal, and 25.6% vs. 3.0% for whole gut transit time). This remained significant when patients with prolonged gastric emptying time were removed from the analysis. No patient had abnormal transit times in all three compartments reported (gastric, small intestinal, and mouth to caecum), suggesting that there was an impact on specific segments of the intestine rather than an overall effect on the whole GI tract. The presence of autonomic neuropathy correlated significantly with delayed gastric emptying, although there was no significant difference in oro-caecal or whole gut transit time in patients with or without autonomic neuropathy. This is in contrast to the work of Scarpello et al., who reported a significant prolongation of oro-caecal transit time in diabetic patients with autonomic neuropathy versus patients without autonomic neuropathy or healthy volunteers (hydrogen appearance time 140.2 min compared to 69.8 or 70.8 min, respectively) (Scarpello et al., 1976). This study was performed in the fasted state.

Increased intestinal permeability has been reported in patients with T1DM and T2DM and in animal models of the disease, as assessed by sugar permeability tests (Vaarala et al., 2008; Zhong et al., 2016). This is attributed to a more permeable mucosal barrier ('leaky gut'), due to intestinal inflammation and altered interepithelial tight junctions caused by hyperglycaemia (Thaiss et al., 2018).

Chronic diarrhoea is a common symptom of diabetes, occurring in 10–22% of patients. 43% of patients presenting chronic diarrhoea show evidence of small intestinal bacterial overgrowth (Virally-Monod et al., 1998). Cuoco et al. demonstrated that treatment of small intestinal bacterial overgrowth with antibiotics accelerated oro-caecal transit time in the majority of diabetic patients (62%) (Cuoco et al., 2002). There is growing evidence that the composition of the intestinal microflora in T2DM patients is different compared to healthy controls, e.g., a lower amount of butyrate-producing bacteria is reported (Tilg and Moschen, 2014). Disbiosis of the microflora caused by, e.g., antibiotic therapies and low-fibre diet, results in reduced production of short-chain fatty acids, which impacts the pathogenesis of T2DM (Aw and Fukuda, 2018).

Antidiabetic agents can also have a significant impact on GI conditions. Metformin is widely prescribed in T2DM, and up to 25% of subjects suffer from GI side effects (McCreight et al., 2016). Its effects on the GI tract were recently reviewed by McCreight et al. (2016); key mechanisms of interest from a biopharmaceutics perspective are briefly summarised here. Metformin increases intestinal glucose uptake, which is the basis of an interaction with the imaging agent F-18-fluorodeoxyglucose. However, the mechanism by which metformin increases glucose uptake is currently unclear. Metformin was also shown to increase glucagon-like peptide 1 (GLP-1) concentration in mice and in humans, probably through an increase in GLP-1 secretion. GLP-1 can slow down gastric emptying (Marathe et al., 2013), although there do not appear to be any reports that directly make this link for metformin. Metformin has structural similarities to 5-hydroxytryptamine agonists, and stimulates the intestinal release of 5-hydroxytryptamine *in vitro*. 5-hydroxytryptamine release in the intestine is associated with nausea, vomiting and diarrhoea, and it is hypothesised that this could be one mechanism responsible for the GI side effects observed with metformin. Finally, metformin increases the concentration of bile acids in the small intestine by reducing their ileal absorption and it alters the gut microbiome in mouse and human.

GLP-1 agonists used to treat T2DM, such as exenatide, have GI side effects including nausea and diarrhoea. These agents can slow down gastric emptying through their pharmacological action on GLP-1 receptors (Marathe et al., 2013). Exenatide administered twice daily delays gastric emptying in a dose-dependent manner; the half-emptying time for the solid component of a test meal was increased by 1.9- and 2.8-fold for 5 µg and 10 µg exenatide doses, respectively, and for the liquid meal components increased by 2.6- and 3.4-fold, respectively (Linnebjerg et al., 2008). The impact of long-acting GLP-1 agonists on

gastric emptying appears to diminish with time, whereas this is not the case for short-acting GLP-1 agonists (Marathe et al., 2013).

In summary, several aspects of GI conditions can differ between diabetic patients and healthy subjects, which could impact drug product performance in this patient group. Delayed gastric emptying could lead to reduced or delayed C_{max} . The longer time spent in the gastric environment could alter dissolution for drugs with pH-dependent solubility, increasing the time available for dissolution of basic compounds in an acidic environment where they are more soluble, and delaying the arrival of weakly acid drugs in the small intestine where the majority of dissolution will occur for these compounds. There could also be an increase in degradation of drugs which are unstable in an acidic environment. Increased rate and extent of absorption may be observed for compounds that normally exhibit permeability-limited absorption. For drugs which are subject to bacterial metabolism (either for activation or clearance), the presence of small intestinal bacterial overgrowth could result in increased bacterial degradation, and occurring at an earlier site in the small intestine before significant absorption has occurred, and the potentially altered microbiome composition could result in different metabolic profiles. The side effects of antidiabetic medications can also affect several aspects of GI functions, representing an additional source of absorption variability in this patient population.

5.4. HIV enteropathy

Patients infected with human immunodeficiency virus (HIV) or patients who develop acquired immunodeficiency syndrome (AIDS) have reduced immune response that often leads to other comorbidities. The most common ones are of GI origin, including symptoms such as diarrhoea, weight loss, vomiting, nausea, and dysphagia (Lim et al., 1993; Malebranche et al., 1983). In addition, patients with HIV/AIDS develop certain types of cancer, among which GI malignancies, more often compared to non-HIV infected patients (Coghill et al., 2015).

HIV enteropathy is a condition characterized by persistent diarrhoea, without a pathogen isolated in the stool (Slavik, 2012). Many theories have been formulated to explain the possible cause(s) of diarrhoea in HIV patients, however it remains unclear.

As previously shown, HIV affects the mucosal immune system of the GI tract mostly during the acute infection period, but then again the influence of HIV on lamina propria immune cells in later stages of the disease is also confirmed (Dikman et al., 2015). Consequently, the number of mucosal CD4+ lymphocytes is reduced as compared with peripheral CD4+ cells in the early stage of HIV infection, and the immune response to usual pathogens decreases (Mehandru et al., 2004). The number of CD4+ T cells correlates well with GI symptoms (Thompson et al., 2012). Mucosal CD4+ cells are more susceptible to depletion in contrast to peripheral CD4+ cells because of the expression of the specific co-receptor CCR5 (Brenchley and Douek, 2008; Poles et al., 2001). Inflammation and damaged epithelium (villous atrophy and blunting and crypt hyperplasia) altogether increase intestinal permeability (Batman et al., 2007; Brenchley and Douek, 2008; Sharpstone et al., 1999). Hence, studies have shown that HIV-positive patients have vitamin B12 deficiency due to the reduced permeation in intestines and steatorrhea as a result of decreased fat absorption (Ehrenpreis et al., 1994). Likewise, the changes in intestinal absorption can reduce the AUC or C_{max} of some antituberculosis drugs, as tuberculosis represents a common comorbidity in HIV-positive patients (Gurumurthy et al., 2004; McIlleron et al., 2012). On the other hand, in HIV-positive patients without chronic diarrhoea, no significant change in plasma concentrations of antituberculosis drugs was observed (van Oosterhout et al., 2015). In addition, proton pump inhibitors or H2 antagonists, often administered to HIV positive patients, can decrease the absorption of antiretroviral agents by changing gastric pH, and consequently drugs solubility (Hughes et al., 2015).

Altered absorption in HIV infected patients may also be caused by

the changes in the microbiota. Recent research suggests that microbiota can be considered as an organ, and as such it has its own pathology that can influence the functioning of other systems (Baquero and Nombela, 2012). HIV causes a decrease in certain types of gut bacteria such as Bacteroides, Lactobacillus and Clostridia. On the other hand, pathogenic bacteria like Prevotella and Proteobacteria are abundant resulting in an imbalance in the gut flora. Furthermore, the altered microbiota induces inflammation that affects the GI mucosa (Zevin et al., 2016). These can potentially lead to changes in drug absorption.

5.5. Critical illness

Critically ill patients often depend on pharmacotherapy, however, they are in a condition in which drug disposition might have changed and pharmacotherapy might become erratic. Although oral drug administration is generally not the preferred route especially for life-saving drugs, there are nevertheless several reasons for selecting oral medications, i.e., absence of intravenous access, higher occurrence of side-effects with intravenous administration, absence of appropriate intravenous formulations (especially for the paediatric population).

Roberts and Hall reviewed drug absorption considerations in critically ill adults and identified mesenteric hypoperfusion, increased intestinal permeability, decreased functional absorptive capacity, and delayed gastric emptying leading to significant changes in oral drug absorption with higher and lower bioavailability (Kar et al., 2015; Roberts and Hall, 2013).

As inflammation has shown to alter drug metabolism and transport in the liver, it can be expected that this is also the case for the intestine (Aitken et al., 2006; Evers et al., 2018; Vet et al., 2016). Indeed, *in vitro* studies also show mostly a decrease in transporter gene and protein expression with inflammatory states as proinflammatory cytokine-induction, high altitude or response to enteropathogenic bacteria (Evers et al., 2018). At the same time, the complexity and interplay of drug metabolizing enzymes and transporters make it difficult at this time to predict the effect on drug bioavailability.

When drugs are given orally to sedated and non-sedated critically ill patients they are most often administered through gastric or duodenal feeding tubes. This might impose problems for some drugs, as the need to be crushed and suspended or dissolved, potentially can reduce stability or induce chemical characteristics resulting in sticking to tubes. Enteral administration and the alteration of the drug product may also significantly modify the rate and/or extent of drug release and absorption causing wide variability in serum concentrations, as described for different antibiotics (Roberts and Hall, 2013). A change in phenytoin plasma levels was found in patients after starting or discontinuing enteral feeding compared to normal oral administration, exposing them to increased risk of seizures. This observation suggests an interaction with enteral feeding, although the mechanism is not fully understood (Au Yeung and Ensom, 2000).

Besides the processes specific to oral absorption, other processes involved in drug disposition (i.e., distribution, metabolism, elimination) may be altered in the critically ill due to, e.g., body fluid shifts, alteration in protein binding or pH, renal or hepatic failure, or the need for life-sustaining measures as extracorporeal membrane oxygenation or dialysis (Thakkar et al., 2017). Polypharmacy is common in the Intensive Care Unit and further contributes to possible changes in oral drug absorption, e.g., by delaying gastric emptying, altering gastric and enteric pH, or inducing drug-drug interactions.

In summary, altered oral drug absorption has been observed in critically ill patients in the past. For these patients there are several disease-, co-medication-, and medical care-related factors that may affect oral exposure. This complexity represents a major challenge in predicting drug absorption or making dosing recommendations in this group of patients.

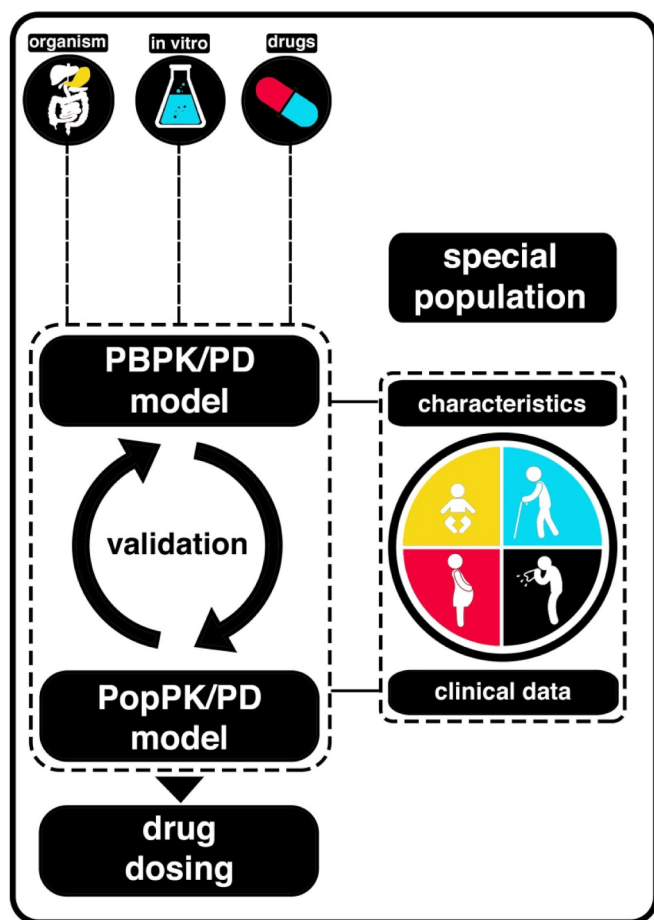


Fig. 4. Schematic illustration of the role of physiologically based and population pharmacokinetic/ pharmacodynamics (PBPK/PD and popPK/PD) models towards guiding drug dosing in special populations.

6. Physiologically based and population pharmacokinetic modelling in special populations

Knowledge of a drug's PK and pharmacodynamics and the relationship between them is required to guide appropriate drug dosing (Standing, 2017). Both of these factors can differ between populations of healthy individuals and patients and in particular, differences in GI physiological function can affect a drug's PK profile and consequently affect drug therapy. Therefore, model informed approaches represent a valuable tool for drug development in special populations (Suri et al., 2015).

PBPK models are mathematical representations of the body, parameterized based on known physiological data such as tissue composition, tissue volumes and blood flows (Jones et al., 2015). PBPK models integrate this physiological description with drug specific data to simulate the time-course of drug concentrations in plasma and tissues. PBPK models can also describe the processes of drug absorption with mechanistic absorption models. Commercial implementations of mechanistic absorption models (Agoram et al., 2001; Jamei et al., 2009) are now routinely used in the pharmaceutical industry to address questions around intrinsic and extrinsic factors influencing oral absorption such as formulation, and both the FDA (FDA, 2018) and the European Medicines Agency (EMA, 2016) have recently produced guidance documents on appropriate use of PBPK models.

Since PBPK models follow a systems pharmacology approach, they

include both system specific and drug specific data where system specific data refers to the physiology being simulated. When sufficient knowledge on the influence of disease or non-disease-related conditions on the GI physiology exists, this may be integrated into the models and the effects predicted. To verify an initially developed PBPK model and its assumptions, predictions should be confirmed with *in vivo* data from early clinical phases and in this context, a population PK (popPK) model which describes these data well, can be useful to refine a PBPK model (Kostewicz et al., 2014). In addition, when clinical data are available, verification of the special population-based PBPK model predictions can be performed (Suri et al., 2015).

PopPK modelling is a statistical approach, typically applied to describe the sources of PK variability in *in vivo* data obtained in clinical studies in both healthy individuals and patients. Although popPK is usually considered a non-mechanistic approach, some physiological parameters can be incorporated in the models such as body size, age or organ function (Schlender et al., 2018). Furthermore, efforts are being undertaken to increase the physiological knowledge included in popPK models to describe the extent and rate of absorption. Due to ethical and practical considerations, patients representing special populations are often underrepresented in clinical trials. Nevertheless, a popPK approach can be applied to optimize study design to obtain optimal PK data.

Several examples of simulations in special populations have been published. Perhaps the most studied is the paediatric population where reviews of the development and maturation of GI physiology have been published and implemented into commercial software platforms (Johnson et al., 2018; Samant et al., 2015). These paediatric absorption models provide an invaluable tool to guide formulation development in children although large gaps in understanding the underlying physiology still exist and verification of the model performance is still limited (Kohlmann et al., 2017; Villiger et al., 2016). Other areas where oral absorption models are being applied is for modelling the influence of food (Tistaert et al., 2019) although effects of different diets is not well explored currently. The effect of changed GI pH on the absorption of ionisable drugs with pH dependent solubility is also studied and existing absorption models can account for these changes which could be relevant in elderly populations, as well as in those taking acid reducing agents as co-medication (Cristofolletti et al., 2017), which is often the case for oncology patients. Within the commercial software tools, specific disease related PBPK models exist for hepatic and renal impairment (Hsueh et al., 2018; Wagner et al., 2017) and for different ethnicities (Barter et al., 2011), but these models include little to no information on differences in absorption between these populations. Publications have also reported PBPK models incorporating specific pathophysiological changes to capture drug-disease PK interactions (Rasool et al., 2015), but there is little done on diseases of the GI tract. For a more thorough review of applications of PBPK to enable personalized medicine a recent paper from Hartmanshenn is recommended (Hartmanshenn et al., 2016).

PBPK and popPK modelling are complementary methods for characterizing and predicting the impact of intrinsic and extrinsic factors on drug exposure. In order to describe and/or predict drug effects and inform special population-based drug dosing, the extension of popPK and PBPK models with a pharmacodynamic component is required (Fig. 4) (Kostewicz et al., 2014; Standing, 2017).

7. How are special populations considered in regulatory guidance?

Typical drug development requires clinical testing of medicines in a general population and can exclude special populations. For example, typical exclusion criteria in phase 1 and 2 trials include: adults aged

Table 1
Regulatory guidelines that provide information on the inclusion of special populations in clinical testing.

Date of introduction	Body responsible	Title of guidance	Population included	Relevant content	Reference
General					
1997	ICH E8	General considerations for clinical trials	-	Obtaining pharmacokinetic information in sub-populations such as patients with impaired elimination (renal or hepatic failure), the elderly, children, women and ethnic subgroups should be considered	(ICH, 1997)
2019	FDA	Population pharmacokinetics	Refers to weight; excretory and metabolic functions; paediatric; elderly; sex	Specifically to highlight the impact of safety and efficacy differences in population sub-groups	(FDA 2019)
2003	FDA	Exposure-response relationships — Study design, data analysis, and regulatory applications	Refers to subpopulations with a specific paediatric decision tree	Links exposure and response to intrinsic and extrinsic patient factors	(FDA, 2003a)
2008	ICH M3	Non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals	-	Makes reference to inclusion of women; pregnant women; paediatric populations	(ICH, 2008)
Sex					
1993	FDA	Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs	Women (including pregnancy)	To investigate sex differences in safety and efficacy of medicines	(FDA, 1993)
2005	EMA	Gender considerations in the conduct of clinical trials	Women included in pivotal clinical trials	Patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug	(EMA, 2005)
2013	Health Canada	Considerations for Inclusion of women in clinical trials and analysis of sex differences	Women included in pivotal clinical trials	Recommendation that a representative number of women are included in clinical trials	(Health Canada, 2013)
Ethnicity					
1998	ICH E5(R1)	Ethnic factors in the acceptability of foreign clinical data	Ethnically different populations	Bridging studies may be required to demonstrate equivalence between ethnic populations (or to justify a dose adjustment)	(ICH, 1998)
Age					
1989	FDA	Guideline for the study of drugs likely to be used in the elderly	Patients aged > 75 years	Attempts should be made to include elderly subjects in clinical trials	(FDA, 1989)
1993	ICH E7	Studies in support of special populations: Geriatrics	Patients aged > 65 years	Meaningful numbers of geriatric patients should be included in Phase 2 and Phase 3 studies	(ICH, 1993)
2000	ICH E11	Clinical investigation of medicinal products in the paediatric population	Patients aged < 18 years	The guideline addressed considerations about when initiating a pediatric program for a medicinal product; timing of initiation of pediatric studies during medicinal product development; types of studies (PK, PK/PD, efficacy, safety); age categories; and ethics of pediatric clinical investigation.	(ICH, 2000)
2007	EMA	Role of pharmacokinetics in the development of medicinal products in the paediatric population	Patients aged < 17 years	This guideline provides advice on the use of PK studies in paediatric drug development and on methodological issues concerning PK studies in paediatric patients	(EMA, 2007)
2009	EMA	Guideline on the investigation of medicinal products in the term and preterm neonate	Patients aged < 27 days (incl. preterm)	The guideline provides guidance for the development of medicinal products for use in the neonatal period.	(EMA, 2009)
2014 (Draft)	FDA	General clinical pharmacology considerations for pediatric studies for drugs and biological products	Patients aged < 16 years	Clinical pharmacology studies in the paediatric population should be conducted in patients receiving therapy for a particular indication, or in rare instances, in those who are at risk for the condition of interest	(FDA 2014)
2017	EMA	Addendum (R1) to the Guideline on clinical investigation of medicinal products in the pediatric population	Patients aged < 18 years	The guidelines provides an approach to the safe, efficient, and ethical study of medicinal products in paediatric patients.	(EMA, 2017)
Disease state					
2003	FDA	Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling	Patients stratified by the three Child-Pugh categories: mild, moderate and severe	To determine whether the PK of a drug and its active metabolites are altered in patients with hepatic impairment to the extent that an adjustment to the dosage would be indicated	(FDA, 2003b)
2005	EMA	Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function	Hepatic dysfunction is categorised (using Child-Pugh) into groups called A, B and C or “Mild”, “Moderate” and “Severe” corresponding to 5-6, 7-9 and 10-15 scores	Provides recommendation on situations when PK studies should be performed in subjects with impaired hepatic function	(EMA, 2005)
2010	FDA				(FDA, 2010)

(continued on next page)

Table 1 (continued)

Date of introduction	Body responsible	Title of guidance	Population included	Relevant content	Reference
2016	EMA	Pharmacokinetics in patients with impaired renal function — Study design, data analysis, and impact on dosing and labeling Evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function	Patients stratified by renal function based on estimated glomerular filtration rate (eGFR) or estimated creatinine clearance (CLcr) Patients stratified by renal function based on GFR	To determine whether the PK of a drug and its active metabolites are altered in patients with renal impairment to the extent that an adjustment to the dosage would be indicated To determine the effect of decreased renal function on drug exposure and to guide dosing recommendations in patients who have altered renal function	(EMA, 2016)
Physiology 2004	FDA	Pharmacokinetics in pregnancy — Study design, data analysis, and impact on dosing and labeling	Pregnant women	Study participants should be representative of a typical patient population for the drug to be studied including race, ethnicity, and trimester of pregnancy.	(FDA, 2004)
2005	FDA	Clinical lactation studies — Study design, data analysis, and recommendations for labeling	Lactating women	Study participants are lactating women who are planning to receive or are currently receiving study medication.	(FDA, 2005)
2018	EMA	Reflection paper on investigation of pharmacokinetics and pharmacodynamics in the obese population	Obese patients stratified by WHO classification of obesity (linked to BMI)	Specific mention of issues in absorption, "Increases in perfusion of the gut and accelerated gastric emptying with subsequent enhancement of drug bioavailability have been reported for the oral route"	(EMA, 2018)

<18 or >65 years; a BMI greater than 30 kg/m²; pregnancy; hepatic dysfunction (Tamboli et al., 2010). Phase 3 trials can have broader recruitment with increased age; increased divergence in ethnicity and inclusion of patients with co-morbidities. Regulatory guidance on special populations has related to differences in PK broadly, yet there is limited focus on the GI and absorption parameters within this recognition. The importance of non-clinical safety studies to support clinical testing in special populations is detailed in the ICH M3 guidance document (ICH, 2008). Clinical testing in special populations is detailed in ICH E8 guidelines (ICH, 1997) and a recent review on special populations in clinical research (Grimsrud et al., 2015).

Regulatory guidance on biopharmaceutics classification system (BCS) based biowaivers do not mention any special populations or allude to any additional risk mitigation; this may cause particular risks for certain special populations (FDA, 2017). In addition, bioequivalence studies are likely to be undertaken in a small population of males aged 18–40 years of the same ethnicity (Western), with a BMI < 30 kg/m² and healthy volunteers (FDA, 2014). Despite regulations stating that a mixture of males and females should be included in bioequivalence studies, there are issues in identifying what proportion of women are involved in some key studies (McGregor et al., 2017). There are differences in the requirements for bioequivalence testing in Japan due to the lower gastric acidity reported in this population (Tamboli et al., 2010). Also the dose number, which is defined as the ratio of drug concentration in the administered volume to its saturation solubility in water, is calculated using a 150 mL volume in Japan rather than the 250 mL volume used in the rest of the world (Takagi et al., 2006). This lower volume accounts for the lower volume of co-administered water in Japanese bioequivalence studies (Kuribayashi et al., 2016).

The paediatric decision tree that was first presented within FDA Guidance on exposure-response relationships (FDA, 2003a) provides a decision tree that might be used also for other special populations in terms of extrapolation of PK data from a healthy adult population. Increasingly, the use of *in vitro* and *in silico* tools to mitigate risks in special populations has been highlighted for paediatric (Batchelor et al., 2013), elderly (Thompson et al., 2009), obese (Ghobadi et al., 2011) and pregnant (Dallmann et al., 2018) populations. These tools are increasingly supported by the regulators to support dose finding for trials or even replace clinical trials in special populations (FDA, 2018).

Table 1 describes the guidance available that mention the inclusion of special populations in clinical testing and the timeline for the introductions is shown in Fig. 5.

8. Conclusions

The process of oral drug absorption is complex and influenced by many compound- and GI physiology-related factors. The present review evidences how different demographic and clinical conditions can influence the environment in the GI tract, and thus, modify the kinetics of drug release and absorption when compared to the situation in a healthy adult (Fig. 6). Consideration of these alterations in GI tract physiology is key to ensure safe and effective use of oral medications. Patient-specific PBPK models and biorelevant *in vitro* tests, which can account for these changes in GI tract physiology, are extremely useful to anticipate oral drug exposure in patient populations. Such predictive tools can support dose finding, formulation selection, as well as the design and conduct of clinical studies. If sufficient confidence in a compound-specific PBPK model is given, it may even be used to waive clinical studies, for example to show bioequivalence between different formulations.

Although multiple studies have already addressed some aspects of GI tract alterations in specific clinical conditions and have highlighted how these changes can impact oral exposure, there still exist significant knowledge gaps in this area. The relevant parameters for oral absorption, such as the volume and composition of GI fluids or the expression level of enzymes and transporters, are often insufficiently characterised,

		1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020																									
	Sex											FDA											EMA											Health Canada																												
	Ethnicity																					ICH E5																																								
Age	Elderly											FDA											ICH E7																																							
	Pediatric																															ICH E11											EMA	EMA											FDA					EMA		
Disease	Hepatic function																															FDA	EMA																													
	Renal function																																																			FDA										
Physiology	Pregnancy																															FDA																														
	Breastfeeding																															FDA																														
	Obesity																																																													EMA

Fig. 5. Timeline of regulations (listed in Table 1) introduced to provide guidance on special populations.

which is limiting, for example, the development of disease-specific PBPK models. Moreover, a clinical condition often implies a particular setting in terms of medication and diet, such as co-medications, crushing of tablets, or co-administration of fibre-rich nutrition in elderly patients, which increases the complexity for anticipating the impact on bioavailability.

Further research is therefore required using new methods and diagnostic tools to generate physiological reference data and improve biopharmaceutics tools to ensure safe and efficacious drug therapies in the targeted patient population.

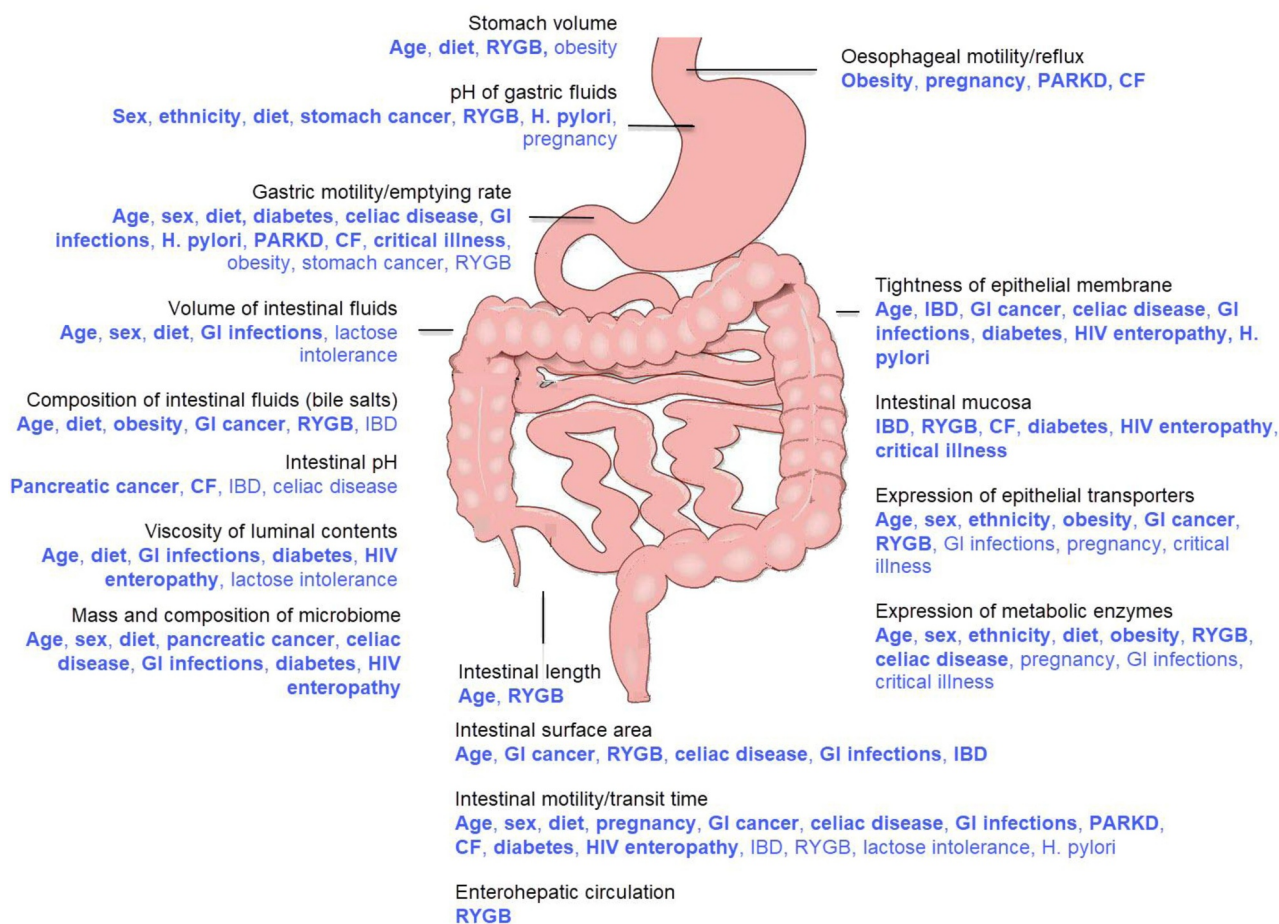


Fig. 6. Overview of the main GI parameters influencing oral drug absorption (black) and the corresponding disease and non-disease related conditions that are known to alter these physiological properties (blue) [RYGB: Roux-en-Y gastric bypass; *H. pylori*: *Helicobacter pylori*; PARKD: Parkinson's disease; CF: Cystic fibrosis; CD: celiac disease; IBD: irritable bowel syndrome; HIV: human immunodeficiency virus].

Credit author statement

All authors contributed equally to this review.

In addition, Cordula Stillhart and Anette Müllertz were responsible for putting the individual parts together and revising the manuscript.

Declarations of Competing Interest

None.

Acknowledgements

This article is based upon work from COST Action UNGAP (CA16205), supported by COST (European Cooperation in Science and Technology).

References

- Abduljalil, K., Furness, P., Johnson, T.N., Rostami-Hodjegan, A., Soltani, H., 2012. Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling. *Clin. Pharmacokinet.* 51, 365–396.
- Abdussalam, A., Al-Agili, M., Al Nebaihi, H.M., Mayo, P.R., Gabr, R.Q., Brocks, D.R., 2018. Dietary-induced obesity and changes in the biodistribution and metabolism of amiodarone in the rat. *J. Pharm. Sci.* 107, 2938–2945.
- Adamska, A., Falasca, M., 2018. ATP-binding cassette transporters in progression and clinical outcome of pancreatic cancer: What is the way forward? *World J. Gastroenterol.* 24, 3222–3238.
- Aebischer, T., Fischer, A., Walduck, A., Schlötelburg, C., Lindig, M., Schreiber, S., Meyer, T., Bereswill, S., Göbel, U., 2006. Vaccination prevents *Helicobacter pylori*-induced alterations of the gastric flora in mice. *FEMS Immunol. Med. Microbiol.* 46, 221–229.
- Afonso-Pereira, F., Dou, L., Trenfield, S.J., Madla, C.M., Murdan, S., Sousa, J., Veiga, F., Basit, A.W., 2018. Sex differences in the gastrointestinal tract of rats and the implications for oral drug delivery. *Eur. J. Pharm. Sci.* 115, 339–344.
- Agoram, B., Woltoz, W.S., Bolger, M.B., 2001. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. *Adv. Drug Deliv. Rev.* 50 (1), S41–S67 Suppl.
- Aitken, A.E., Richardson, T.A., Morgan, E.T., 2006. Regulation of drug-metabolizing enzymes and transporters in inflammation. *Annu. Rev. Pharmacol. Toxicol.* 46, 123–149.
- Amidon, S., Brown, J.E., Dave, V.S., 2015. Colon-targeted oral drug delivery systems: design trends and approaches. *AAPS PharmSciTech* 16, 731–741.
- Ashiru, D.A., Patel, R., Basit, A.W., 2008. Polyethylene glycol 400 enhances the bioavailability of a BCS class III drug (ranitidine) in male subjects but not females. *Pharm. Res.* 25, 2327–2333.
- Asik, M., Gunes, F., Binnetoglu, E., Eroglu, M., Bozkurt, N., Sen, H., Akbal, E., Bakar, C., Beyazit, Y., Ukinc, K., 2014. Decrease in TSH levels after lactose restriction in Hashimoto's thyroiditis patients with lactose intolerance. *Endocrine* 46, 279–284.
- Au Yeung, S.C., Ensom, M.H., 2000. Phenytoin and enteral feedings: does evidence support an interaction? *Ann. Pharmacoth.* 34, 896–905.
- Aw, W., Fukuda, S., 2018. Understanding the role of the gut ecosystem in diabetes mellitus. *J. Diabetes Investig.* 9, 5–12.
- Bai, J.P.F., Burckart, G.J., Mulberg, A.E., 2016. Literature review of gastrointestinal physiology in the elderly, in pediatric patients, and in patients with gastrointestinal diseases. *J. Pharm. Sci.* 105 (2), 476–483.
- Banerjee, A., Pathak, S., Subramaniam, V.D., G, D., Murugesan, R., Verma, R.S., 2017. Strategies for targeted drug delivery in treatment of colon cancer: current trends and future perspectives. *Drug Discov. Today* 22, 1224–1232.
- Baquero, F., Nombela, C., 2012. The microbiome as a human organ. *Clin. Microbiol. Inf.* 18 (4), 2–4 Suppl.
- Barkas, F., Liberopoulos, E., Kei, A., Elisaf, M., 2013. Electrolyte and acid-base disorders in inflammatory bowel disease. *Ann. Gastroenterol.* 26, 23–28.
- Barnes, G.L., Townley, R.R.W., 1973. Duodenal mucosal damage in 31 infants with gastroenteritis. *Arch. Dis. Child.* 48, 343.
- Barter, Z., Yeo, R., Tucker, G., 2011. Prediction of differences in pharmacokinetics between chinese and caucasian populations using a mechanistic physiologically-based pharmacokinetic model. In: 4th Asian Pacific Regional International Society for the Study Of Xenobiotics Meeting.
- Bassotti, G., Antonelli, E., Villanacci, V., Baldoni, M., Dore, M.P., 2014. Colonic motility in ulcerative colitis. *United European Gastroenterol. J.* 2, 457–462.
- Bassotti, G., Villanacci, V., Mazzocchi, A., Mariano, M., Incardona, P., Clerici, C., Morelli, A., 2008. Antroduodenal motor activity in untreated and treated celiac disease patients. *J. Gastroenterol. Hepatol.* 23, e23–e28.
- Batchelor, H., Kaukonen, A.M., Klein, S., Davit, B., Ju, R., Ternik, R., Heimbach, T., Lin, W., Wang, J., Storey, D., 2018. Food effects in paediatric medicines development for products co-administered with food. *Int. J. Pharm.* 536, 530–535.
- Batchelor, H.K., Fotaki, N., Klein, S., 2014. Paediatric oral biopharmaceutics: key considerations and current challenges. *Adv. Drug Deliv. Rev.* 73, 102–126.
- Batchelor, H.K., Kendall, R., Desset-Brethes, S., Alex, R., Ernest, T.B., 2013. Application of in vitro biopharmaceutical methods in development of immediate release oral dosage forms intended for paediatric patients. *Eur. J. Pharm. Biopharm.* 85, 833–842.
- Batman, P.A., Kotler, D.P., Kapembwa, M.S., Booth, D., Potten, C.S., Orenstein, J.M., Scally, A.J., Griffin, G.E., 2007. HIV enteropathy: crypt stem and transit cell hyperproliferation induces villous atrophy in HIV/Microsporidia-infected jejunal mucosa. *Aids* 21, 433–439.
- Becker, D., Zhang, J., Heimbach, T., Penland, R.C., Wanke, C., Shimizu, J., Kulmatycki, K., 2014. Novel orally swallowable IntelliCap(RR) device to quantify regional drug absorption in human GI tract using diltiazem as model drug. *AAPS PharmSciTech* 15, 1490–1497.
- Becquemont, L., Verstuyft, C., Kerb, R., Brinkmann, U., Lebot, M., Jaillon, P., Funck-Brentano, C., 2001. Effect of grapefruit juice on digoxin pharmacokinetics in humans. *Clin. Pharmacol. Ther.* 70 (4), 311–316.
- Beery, A.K., Zucker, I., 2011. Sex bias in neuroscience and biomedical research. *Neurosci. Behav. Res.* 35, 565–572.
- Behrns, K.E., Smith, C.D., Sarr, M.G., 1994. Prospective evaluation of gastric acid secretion and cobalamin absorption following gastric bypass for clinically severe obesity. *Dig. Dis. Sci.* 39, 315–320.
- Bekusova, V.V., Falchuk, E.L., Okorokova, L.S., Kruglova, N.M., Nozdrachev, A.D., Markov, A.G., 2018. Increased paracellular permeability of tumor-adjacent areas in 1,2-dimethylhydrazine-induced colon carcinogenesis in rats. *Cancer Biol. Med.* 15, 251–259.
- Benini, F., Mora, A., Turini, D., Bertolazzi, S., Lanzarotto, F., Ricci, C., Villanacci, V., Barbara, G., Stanghellini, V., Lanzini, A., 2012. Slow gallbladder emptying reverts to normal but small intestinal transit of a physiological meal remains slow in celiac patients during gluten-free diet. *Neurogastroenterology and Motility.* 24 (100-107), e179–e180.
- Bennink, R., Peeters, M., Van den Maegdenbergh, V., Geypens, B., Rutgeerts, P., De Roo, M., Mortelmans, L., 1998. Comparison of total and compartmental gastric emptying and antral motility between healthy men and women. *Eur. J. Nucl. Med.* 25, 1293–1299.
- Berggren, S., Gall, C., Wollnitz, N., Ekelund, M., Karlsson, U., Hoogstraate, J., Schrenk, D., Lennernäs, H., 2007. Gene and protein expression of P-glycoprotein, MRP1, MRP2, and CYP3A4 in the small and large human intestine. *Mol. Pharm.* 4 (2), 252–257.
- Bergstrom, C.A., Holm, R., Jorgensen, S.A., Andersson, S.B., Artursson, P., Beato, S., Borde, A., Box, K., Brewster, M., Dressman, J., Feng, K.I., Halbert, G., Kostewicz, E., McAllister, M., Muenster, U., Thinnies, J., Taylor, R., Mullertz, A., 2014. Early pharmaceutical profiling to predict oral drug absorption: current status and unmet needs. *Eur. J. Pharm. Sci.* 57, 173–199.
- Beringer, P.M., Owens, H., Nguyen, A., Benitez, D., Rao, A., D'Argenio, D.Z., 2012. Pharmacokinetics of doxycycline in adults with cystic fibrosis. *Antimicrob. Agents Chemother.* 56, 70–74.
- Bezerra, J.A., Thompson, S.H., Morse, M., Koldovsky, O., Udall, J.N., 1990. Intestinal permeability to intact lactose in newborns and adults. *Biol. Neonate.* 58, 334–342.
- Bilborough, J., Targan, S.R., Snapper, S.B., 2016. Therapeutic targets in inflammatory bowel disease: current and future. *Am. J. Gastroenterol.* 3, 27 Supplements.
- Blake, M.J., Abdel-Rahman, S.M., Pearce, R.E., Leeder, J.S., Kearns, G.L., 2006. Effect of diet on the development of drug metabolism by cytochrome P-450 enzymes in healthy infants. *Pediatr. Res.* 60, 717–723.
- Bolme, P., Margareta, E., 1975. Influence of diarrhea on the oral absorption of penicillin V and ampicillin in children. *Scand. J. Infect. Dis.* 7, 141–145.
- Bonner, J.J., Vajjah, P., Abduljalil, K., Jamei, M., Rostami-Hodjegan, A., Tucker, G.T., Johnson, T.N., 2015. Does age affect gastric emptying time? A model-based meta-analysis of data from premature neonates through to adults. *Biopharm. Drug Dispos.* 36, 245–257.
- Bowen, S., Hull, J., 2015. The basic science of cystic fibrosis. *J. Paediatr. Child Health* 25, 159–164.
- Brandt, L.E.F., 2013. The prevalence and growth of obesity and obesity related illnesses in Europe. European Center for International Political Economy, Geneva.
- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: Cancer J. Clin.* 68, 394–424.
- Brenchley, J.M., Douek, D.C., 2008. HIV infection and the gastrointestinal immune system. *Mucosal Immunol.* 1, 23–30.
- Broe, A., Pottegard, A., Lamont, R.F., Jorgensen, J.S., Damkier, P., 2014. Increasing use of antibiotics in pregnancy during the period 2000–2010: prevalence, timing, category, and demographics. *BJOG* 121, 988–996.
- Brogna, A., Ferrara, R., Bucci, A.M., Lanteri, E., Catalano, F., 1999. Influence of aging on gastrointestinal transit time. An ultrasonographic and radiologic study. *Invest. Radiol.* 34, 357–359.
- Brouwer, K.L.R., Aleksunes, L.M., Brandys, B., Giacomini, G.P., Knipp, G., Lukacova, V., Meibohm, B., Nigam, S.M., Rieder, M., Wildt, S.D., 2015. Human ontogeny of drug transporters: review and recommendations of the pediatric transporter working group. *Clin. Pharmacol. Ther.* 98, 266–287.
- Brussee, J.M., Yu, H., Kerkels, E.H.J., de Roos, B., Brill, M.J.E., van den Anker, J.N., Rostami-Hodjegan, A., de Wildt, S.N., Knibbe, C.A.J., 2018a. First-pass CYP3A-mediated metabolism of midazolam in the gut wall and liver in preterm neonates. *CPT Pharmacometrics Syst. Pharmacol.* 7, 374–383.
- Brussee, J.M., Yu, H., Kerkels, E.H.J., Palic, S., Brill, M.J.E., Barrett, J.S., Rostami-Hodjegan, A., de Wildt, S.N., Knibbe, C.A.J., 2018b. Characterization of intestinal and hepatic CYP3A-mediated metabolism of midazolam in children using a physiological population pharmacokinetic modelling approach. *Pharm. Res.* 35, 182.
- Buchholz, V., Berkenstadt, H., Goitein, D., Dickman, R., Bernstein, H., Rubin, M., 2013. Gastric emptying is not prolonged in obese patients. *Surg. Obes. Relat. Dis.* 9, 714–717.
- Budzynski, J., Klopocka, M., 2014. Brain-gut axis in the pathogenesis of *Helicobacter pylori* infection. *World J. Gastroenterol.* 20, 5212–5225.

- Buggins, T.R., Dickinson, P.A., Taylor, G., 2007. The effects of pharmaceutical excipients on drug disposition. *Adv. Drug Deliv. Rev.* 59, 1482–1503.
- Calcagno, A.M., Ludwig, J.A., Fostel, J.M., Gottesman, M.M., Ambudkar, S.V., 2006. Comparison of drug transporter levels in normal colon, colon cancer, and Caco-2 cells: impact on drug disposition and discovery. *Mol. Pharm.* 3, 87–93.
- Camilleri, M., Malhi, H., Acosta, A., 2017. Gastrointestinal complications of obesity. *Gastroenterology* 152, 1656–1670.
- Health Canada, 2013. Guidance document: considerations for inclusion of women in clinical trials and analysis of sex differences. <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/considerations-inclusion-women-clinical-trials-analysis-data-sex-differences.html> (accessed 11. September 2019).
- Carrión, S., Clavé, P., 2017. Gastrointestinal disease in the older population. In: Michel, J.P., Beattie, B.L., Martin, F.C., Walston, J. (Eds.), *Oxford Textbook of Geriatric Medicine*, 3rd ed. Oxford University Press, Oxford, United Kingdom, pp. 1110.
- Carswell, K.A., Vincent, R.P., Belgaumkar, A.P., Sherwood, R.A., Amiel, S.A., Patel, A.G., le Roux, C.W., 2014. The effect of bariatric surgery on intestinal absorption and transit time. *Obes. Surg.* 24, 796–805.
- Cascorbi, I., 2006. Role of pharmacogenetics of ATP-binding cassette transporters in the pharmacokinetics of drugs. *Pharmacol. Therapeut.* 112, 457–473.
- Cellini, M., Santaguida, M.G., Gatto, I., Virili, C., Del Duca, S.C., Brusca, N., Capriello, S., Gargano, L., Centanni, M., 2014. Systematic appraisal of lactose intolerance as cause of increased need for oral thyroxine. *J. Clin. Endocrinol. Metab.* 99, E1454–E1458.
- Centanni, M., Gargano, L., Canettieri, G., Viceconti, N., Franchi, A., Delle Fave, G., Annibale, B., 2006. Thyroxine in goiter, *Helicobacter pylori* infection, and chronic gastritis. *N. Engl. J. Med.* 354, 1787–1795.
- Chang, F.Y., Chen, C.Y., Lu, C.L., Luo, J.C., Jiun, K.L., Lee, S.D., Wu, C.W., 2004. Undisturbed water gastric emptying in patients of stomach cancer. *Hepato-Gastroenterology* 51, 1219–1224.
- Chang, J., Rayner, C.K., Jones, K.L., Horowitz, M., 2010. Diabetic gastroparesis and its impact on glycemia. *Endocrin. Metabol. Clin.* 39, 745–762.
- Chen, L., Prasad, G.V.R., 2018. CYP3A5 polymorphisms in renal transplant recipients: influence on tacrolimus treatment. *Pharmacogenomics Pers. Med.* 11, 23–33.
- Chen, M.L., 2006. Ethnic or racial differences revisited: impact of dosage regimen and dosage form on pharmacokinetics and pharmacodynamics. *Clin. Pharmacokinet.* 45, 957–964.
- Cheung, K.W.K., Van Groen, B.D., Burckart, G.J., Zhang, L., de Wildt, S.N., Huang, S.M., 2019. Incorporating ontogeny in physiologically based pharmacokinetic modeling to improve pediatric drug development: What we know about developmental changes in membrane transporters. *J. Clin. Pharm.* 59, S56–S69.
- Chiarioni, G., Bassotti, G., Germani, U., Battaglia, E., Brentegani, M.T., Morelli, A., Vantini, I., 1997. Gluten-free diet normalizes mouth-to-cecum transit of a caloric meal in adult patients with celiac disease. *Digest. Dis. Sci.* 42, 2100–2105.
- Chiloiri, M., Darconza, G., Piccoli, E., De Carne, M., Clemente, C., Riezzo, G., 2001. Gastric emptying and oro-cecal transit time in pregnancy. *J. Gastroenterol.* 36, 538–543.
- Ciacchio, E.J., Bhagat, G., Lewis, S.K., Green, P.H., 2016. Recommendations to quantify villous atrophy in video capsule endoscopy images of celiac disease patients. *World J. Gastrointest. Endosc.* 8, 653–662.
- Cichero, J.A., 2013. Thickening agents used for dysphagia management: effect on bioavailability of water, medication and feelings of satiety. *Nutr. J.* 12, 54.
- Coghill, A.E., Shiels, M.S., Suneja, G., Engels, E.A., 2015. Elevated cancer-specific mortality among HIV-infected patients in the United States. *J. Clin. Oncol.* 33, 2376–2383.
- Collett, A., Stephens, R.H., Harwood, M.D., Humphrey, M., Dallman, L., Bennett, J., Davis, J., Carlson, G.L., Warhurst, G., 2008. Investigation of regional mechanisms responsible for poor oral absorption in humans of a modified release preparation of the alpha-adrenoreceptor antagonist, 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroquinolin-2-yl)-5-(2-pyridyl)quinazoline (UK-338,003): the rational use of ex vivo intestine to predict in vivo absorption. *Drug Metab. Dispos.* 36, 87–94.
- Corral, J.E., Dye, C.W., Mascarenhas, M.R., Barkin, J.S., Salathe, M., Moshiree, B., 2016. Is gastroparesis found more frequently in patients with cystic fibrosis? A systematic review. *Scientifica* 2016, 2918139.
- Costantine, M.M., 2014. Physiologic and pharmacokinetic changes in pregnancy. *Front. Pharmacol.* 5, 65.
- Cristofolletti, R., Patel, N., Dressman, J.B., 2017. Assessment of bioequivalence of weak base formulations under various dosing conditions using physiologically based pharmacokinetic simulations in virtual populations. Case examples: ketoconazole and posaconazole. *J. Pharm. Sci.* 106, 560–569.
- Cross, T.L., Kasahara, K., Rey, F.E., 2018. Sexual dimorphism of cardiometabolic dysfunction: Gut microbiome in the play? *Mol. Metab.* 15, 70–81. <https://doi.org/10.1016/j.molmet.2018.05.016>.
- Cui, H., Zhang, A.J., McKeage, M.J., Nott, L.M., Geraghty, D., Guven, N., Liu, J.J., 2017. Copper transporter 1 in human colorectal cancer cell lines: Effects of endogenous and modified expression on oxaliplatin cytotoxicity. *J. Inorg. Biochem.* 177, 249–258.
- Cuoco, L., Montalto, M., Jorizzo, R.A., Santarelli, L., Arancio, F., Cammarota, G., Gasbarrini, G., 2002. Eradication of small intestinal bacterial overgrowth and oro-cecal transit in diabetics. *Hepato-Gastroenterology* 49, 1582–1586.
- Da Silva, C.G., Honeywell, R.J., Dekker, H., Peters, G.J., 2015. Physicochemical properties of novel protein kinase inhibitors in relation to their substrate specificity for drug transporters. *Expert Opin. Drug Metab. Toxicol.* 11, 703–717.
- Dallmann, A., Solodenko, J., Ince, I., Eissing, T., 2018. Applied concepts in PBPK modeling: how to extend an open systems pharmacology model to the special population of pregnant women. *CPT: Pharmacometr. Syst. Pharmacol.* 7, 419–431.
- Darwich, A.S., Pade, D., Ammori, B.J., Jamei, M., Ashcroft, D.M., Rostami-Hodjegan, A., 2012. A mechanistic pharmacokinetic model to assess modified oral drug bioavailability post bariatric surgery in morbidly obese patients: interplay between CYP3A gut wall metabolism, permeability and dissolution. *J. Pharm. Pharmacol.* 64, 1008–1024.
- De Smet, J., Van Bocxlaer, J., Boussery, K., 2013. The influence of bypass procedures and other anatomical changes in the gastrointestinal tract on the oral bioavailability of drugs. *J. Clin. Pharmacol.* 53, 361–376.
- Deal, R.A., Tang, Y., Fletcher, R., Torquati, A., Omotosho, P., 2018. Understanding intestinal glucose transporter expression in obese compared to non-obese subjects. *Surg. Endosc.* 32, 1755–1761.
- Deleu, D., Ebinger, G., Michotte, Y., 1991. Clinical and pharmacokinetic comparison of oral and duodenal delivery of levodopa/carbidopa in patients with Parkinson's disease with a fluctuating response to levodopa. *Eur. J. Clin. Pharmacol.* 41, 453–458.
- Deligiannidis, K.M., Byatt, N., Freeman, M.P., 2014. Pharmacotherapy for mood disorders in pregnancy: a review of pharmacokinetic changes and clinical recommendations for therapeutic drug monitoring. *J. Clin. Psychopharmacol.* 34, 244–255.
- Deng, J., Zhu, X., Chen, Z., Fan, C.H., Kwan, H.S., Wong, C.H., Shek, K.Y., Zuo, Z., Lam, T.N., 2017. A review of food-drug interactions on oral drug absorption. *Drugs* 77, 1833–1855.
- Derakhshankhah, H., Izadi, Z., Alaei, L., Lotfabadi, A., Saboury, A.A., Dinavand, R., Divsalar, A., Seyedarabi, A., Barzegari, E., Evini, M., 2017. Colon cancer and specific ways to deliver drugs to the large intestine. *Anticancer Agents Med. Chem.* 17, 1317–1327.
- Devriese, S., Van den Bossche, L., Van Welden, S., Holvoet, T., Pinheiro, I., Hindryckx, P., De Vos, M., Laukens, D., 2017. T84 monolayers are superior to Caco-2 as a model system of colonocytes. *Histochem. Cell Biol.* 148, 85–93.
- Di Cagno, R., De Angelis, M., De Pasquale, I., Ndajijimana, M., Vernocchi, P., Ricciuti, P., Gagliardi, F., Laghi, L., Crechio, C., Guerzoni, M.E., Gobetti, M., Francavilla, R., 2011. Duodenal and faecal microbiota of celiac children: molecular, phenotype and metabolome characterization. *BMC Microbiol.* 11, 219.
- Diakidou, A., Vertzoni, M., Goumas, K., Soderling, E., Abrahamsson, B., Dressman, J., Reppas, C., 2009. Characterization of the contents of ascending colon to which drugs are exposed after oral administration to healthy adults. *Pharm. Res.* 26, 2141–2151.
- Dikman, A.E., Schonfeld, E., Srisarajivakul, N.C., Poles, M.A., 2015. Human immunodeficiency virus-associated diarrhea: still an issue in the era of antiretroviral therapy. *Dig. Dis. Sci.* 60, 2236–2245.
- Dirksen, C., Dangaard, M., Bojsen-Moller, K.N., Jorgensen, N.B., Kielgast, U., Jacobsen, S.H., Naver, L.S., Worm, D., Holst, J.J., Madsbad, S., Hansen, D.L., Madsen, J.L., 2013. Fast pouch emptying, delayed small intestinal transit, and exaggerated gut hormone responses after Roux-en-Y gastric bypass. *Neurogastroenterol. Motil.* 25, 346–e255.
- Dou, L., Mai, Y., Madla, C.M., Orlu, M., Basit, A.W., 2018. P-glycoprotein expression in the gastrointestinal tract of male and female rats is influenced differently by food. *Eur. J. Pharm. Sci.* 123, 569–575.
- Downey, L., Houten, R., Murch, S., Longson, D., 2015. Recognition, assessment, and management of coeliac disease: summary of updated NICE guidance. *BMJ* 351, h4513.
- Dressman, J.B., Reppas, C., 2010. Oral Drug Absorption: Prediction and Assessment, second ed. CRC Press.
- Drewe, J., Beglinger, C., Kissel, T., 1992. The absorption site of cyclosporin in the human gastrointestinal tract. *Br. J. Clin. Pharm.* 33, 39–43.
- Drozdzik, M., Busch, D., Lapczuk, J., Muller, J., Ostrowski, M., Kurzawski, M., Oswald, S., 2018. Protein abundance of clinically relevant drug-metabolizing enzymes in the human liver and intestine: a comparative analysis in paired tissue specimens. *Clin. Pharmacol. Ther.* 104, 515–524.
- Drozdzik, M., Groer, C., Penski, J., Lapczuk, J., Ostrowski, M., Lai, Y., Prasad, B., Unadkat, J.D., Siegmund, W., Oswald, S., 2014. Protein abundance of clinically relevant multidrug transporters along the entire length of the human intestine. *Mol. Pharm.* 11, 3547–3555.
- Duffield, R.A., 1996. Cystic fibrosis and the gastrointestinal tract. *J. Pediatr. Health Care.* 10, 51–57.
- Eades, S., Boineau, F., Christensen, M., 2000. Increased tacrolimus levels in a pediatric renal transplant patient attributed to chronic diarrhea. *Pediatr. Transplant.* 4, 63–66.
- Edwards, M., Dai, R., Ahmed, S.A., 2018. Our Environment Shapes Us: The Importance of environment and sex differences in regulation of autoantibody production. *Front. Immunol.* 9, 478.
- Effinger, A., O'Driscoll, C.M., McAllister, M., Fotaki, N., 2019. Impact of gastrointestinal disease states on oral drug absorption - implications for formulation design - a PEARL review. *J. Pharm. Pharmacol.* 71, 674–698.
- Ehrenpreis, E.D., Carlson, S.J., Boorstein, H.L., Craig, R.M., 1994. Malabsorption and deficiency of vitamin B12 in HIV-infected patients with chronic diarrhea. *Dig. Dis. Sci.* 39, 2159–2162.
- El-Omar, E.M., 2006. Mechanisms of increased acid secretion after eradication of *Helicobacter pylori* infection. *Gut* 55, 144–146.
- El-Serag, H.B., Tran, T., Richardson, P., Ergun, G., 2006. Anthropometric correlates of intra-gastric pressure. *Scand. J. Gastroenterol.* 41, 887–891.
- Elborn, J.S., 2016. Cystic fibrosis. *Lancet* 388, 2519–2531.
- Elli, L., Bardella, M.T., 2005. Motility disorders in patients with celiac disease. *Scand. J. Gastroenterol.* 40, 743–749.
- EMA, 2005a. Evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. https://www.ema.europa.eu/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-impaired-hepatic-function_en.pdf (accessed 11 September 2019).
- EMA, 2005b. Gender considerations in the conduct of clinical trials. https://www.ema.europa.eu/documents/scientific-guideline/ich-gender-considerations-conduct-clinical-trials-step-5_en.pdf (accessed 11 September 2019).

- EMA, 2007. Role of pharmacokinetics in the development of medicinal products in the paediatric population. https://www.ema.europa.eu/documents/scientific-guideline/guideline-role-pharmacokinetics-development-medicinal-products-paediatric-population_en.pdf (accessed 11 September 2019).
- EMA, 2009. Guideline on the investigation of medicinal products in the term and preterm neonate. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-medicinal-products-term-preterm-neonate-first-version_en.pdf (accessed 29 September 2019).
- EMA, 2016a. Evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function. https://www.ema.europa.eu/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-decreased-renal-function_en.pdf (accessed 11 September 2019).
- EMA, 2016b. Guideline on the qualification and reporting of 4 physiologically based pharmacokinetic (PBPK) modelling and simulation. https://www.ema.europa.eu/documents/scientific-guideline/guideline-qualification-reporting-physiologically-based-pharmacokinetic-pbpb-modelling-simulation_en.pdf (accessed 11 September 2019).
- EMA, 2017. ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e11r1-guideline-clinical-investigation-medicinal-products-pediatric-population-revision-1_en.pdf (accessed 29 September 2019).
- Emerging Risk Factors Collaboration, Sarwar, N., Gao, P., Seshasai, S.R., Gobin, R., Kaptoge, S., Di Angelantonio, E., Ingelsson, E., Lawlor, D.A., Selvin, E., Stampfer, M., Stehouwer, C.D., Lewington, S., Pennells, L., Thompson, A., Sattar, N., White, I.R., Ray, K.K., Danesh, J., 2010. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 375, 2215–2222.
- Enright, E., Gahan, C.M., Joyce, S., Griffin, B., 2016. The impact of the gut microbiota on drug metabolism and clinical outcome. *Yale J. Biol. Med.* 89, 375–382.
- Estudante, M., Morais, J.G., Soveral, G., Benet, L.Z., 2013. Intestinal drug transporters: an overview. *Adv. Drug Del. Rev.* 65, 1340–1356.
- Evans, D.F., Pye, G., Bramley, R., Clark, A.G., Dyson, T.J., Hardcastle, J.D., 1988. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut* 29, 1035–1041.
- Evers, R., Piquette-Miller, M., Polli, J.W., Russel, F.G.M., Sprowl, J.A., Tohyama, K., Ware, J.A., de Wildt, S.N., Xie, W., Brouwer, K.L.R., International Transporter, C., 2018. Disease-associated changes in drug transporters may impact the pharmacokinetics and/or toxicity of drugs: a white paper from the international transporter consortium. *Clin. Pharmacol. Ther.* 104, 900–915.
- Fakhoury, M., Litalien, C., Medard, Y., Cave, H., Ezzahir, N., Peuchmaur, M., Jacqz-Aigrain, E., 2005. Localization and mRNA expression of CYP3A and P-glycoprotein in human duodenum as a function of age. *Drug Metab. Dispos.* 33, 1603–1607.
- Fallahi, P., Ferrari, S.M., Marchi, S., De Bortoli, N., Ruffilli, I., Antonelli, A., 2017. Patients with lactose intolerance absorb liquid levothyroxine better than tablet levothyroxine. *Endocrine* 57, 175–178.
- Falony, G., Vandeputte, D., Caenepel, C., Vieira-Silva, S., Daryoush, T., Vermeire, S., Raes, J., 2019. The human microbiome in health and disease: hype or hope. *Acta Clin. Belg.* 74, 53–64.
- Fasano, A., Visanji, N.P., Liu, L.W., Lang, A.E., Pfeiffer, R.F., 2015. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol* 14, 625–639.
- EMA, 2018. Reflection paper on investigation of pharmacokinetics and pharmacodynamics in the obese population. https://www.ema.europa.eu/documents/scientific-guideline/reflection-paper-investigation-pharmacokinetics-pharmacodynamics-obese-population_en.pdf (accessed 11 September 2019).
- FDA, 1989. Guideline for the study of drugs likely to be used in the elderly. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072048.pdf> (accessed 11 September 2019).
- FDA, 1993. Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs. <https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM131204.pdf> (accessed 11 September 2019).
- FDA, 1994. Prograf® (tacrolimus) capsules. FDA prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050709s031lbl.pdf (accessed 11 September 2019).
- FDA, 2019. Population Pharmacokinetics. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137.pdf> (accessed 11 September 2019).
- FDA, 2002. Guidance for Industry - Food-effect bioavailability and fed bioequivalence studies. <https://www.fda.gov/media/70945/download> (accessed 11 September 2019).
- FDA, 2003a. Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf> (accessed 11 September 2019).
- FDA, 2003b. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf> (accessed 11 September 2019).
- FDA, 2003c. CRESTOR (rosuvastatin calcium) tablets. FDA prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021366s016lbl.pdf (accessed 11 September 2019).
- FDA, 2004. Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072133.pdf> (accessed 11 September 2019).
- FDA, 2005. Clinical Lactation Studies - Study Design, Data Analysis, and Recommendations for Labeling. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072097.pdf> (accessed 11 September 2019).
- FDA, 2010. Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf> (accessed 11 September 2019).
- FDA, 2014. General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf> (accessed 11 September 2019).
- FDA, 2014. Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf> (accessed 11 September 2019).
- FDA, 2017. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Guidance for Industry. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf> (accessed 11 September 2019).
- FDA, 2018. Physiologically Based Pharmacokinetic Analyses - Format and Content. Guidance for industry. <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm531207.pdf> (accessed 11 September 2019).
- Feig, C., Gopinathan, A., Neesee, A., Chan, D.S., Cook, N., Tuveson, D.A., 2012. The pancreas cancer microenvironment. *Clin. Cancer Res* 18, 4266–4276.
- Feldman, M., Barnett, C., 1991. Fasting gastric pH and its relationship to true hypochlorhydria in humans. *Dig. Dis. Sci.* 36, 866–869.
- Fiorini, G., Bland, J.M., Hughes, E., Castelli, V., Vaira, D., 2015. A systematic review on drugs absorption modifications after eradication in *Helicobacter pylori* positive patients undergoing replacement therapy. *J. Gastrointest. Liver Dis.* 24, 95–100 101 p following 100.
- Fischer, J.H., Sarto, G.E., Hardman, J., Endres, L., Jenkins, T.M., Kilpatrick, S.J., Jeong, H., Geller, S., Deyo, K., Fischer, P.A., Rodvold, K.A., 2014. Influence of gestational age and body weight on the pharmacokinetics of labetalol in pregnancy. *Clin. Pharmacokinet.* 53, 373–383.
- Fischer, M., Fadda, H.M., 2016. The effect of sex and age on small intestinal transit times in humans. *J. Pharm. Sci.* 105 (2), 682–686.
- Fleisher, D., Li, C., Zhou, Y., Pao, L.H., Karim, A., 1999. Drug, meal and formulation interactions influencing drug absorption after oral administration. *Clinical implications.* *Clin. Pharmacokinet.* 36, 233–254.
- Ford, R.P., Menzies, I.S., Phillips, A.D., Walker-Smith, J.A., Turner, M.W., 1985. Intestinal sugar permeability: relationship to diarrhoeal disease and small bowel morphology. *J. Pediatr. Gastroenterol. Nutr.* 4, 568–574.
- Freire, A.C., Basit, A.W., Choudhary, R., Piong, C.W., Merchant, H.A., 2011. Does sex matter? The influence of gender on gastrointestinal physiology and drug delivery. *Int. J. Pharm.* 415, 15–28.
- GAO, 2001. Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risk for Women. United States General Accounting Office, Washington.
- Gelfond, D., Borowitz, D., 2013. Gastrointestinal complications of cystic fibrosis. *Clin. Gastroenterol. Hepatol.* 11, 333–342 quiz e330–331.
- Geliebter, A., Hashim, S.A., 2001. Gastric capacity in normal, obese, and bulimic women. *Physiol. Behav.* 74, 743–746.
- Gerards, C., Leodolter, A., Glasbrenner, B., Malfertheiner, P., 2001. H. pylori infection and visceral hypersensitivity in patients with irritable bowel syndrome. *Dig. Dis* 19, 170–173. <https://doi.org/10.1159/000050673>.
- Gesquiere, L., Darwich, A.S., Van der Schueren, B., de Hoon, J., Lannoo, M., Matthys, C., Rostami, A., Foulon, V., Augustijns, P., 2015. Drug disposition and modelling before and after gastric bypass: immediate and controlled-release metoprolol formulations. *Br. J. Clin. Pharmacol.* 80, 1021–1030.
- Gesquiere, L., Hens, B., Van der Schueren, B., Mols, R., de Hoon, J., Lannoo, M., Matthys, C., Foulon, V., Augustijns, P., 2016. Drug disposition before and after gastric bypass: fenofibrate and posaconazole. *Br. J. Clin. Pharmacol.* 82, 1325–1332.
- Ghobadi, C., Johnson, T.N., Aarabi, M., Almond, L.M., Allabi, A.C., Rowland-Yeo, K., Jamei, M., Rostami-Hodjegan, A., 2011. Application of a systems approach to the bottom-up assessment of pharmacokinetics in obese patients: expected variations in clearance. *Clin. Pharmacokinet.* 50, 809–822.
- Ghosh, T., Lewis, D.I., Axon, A.T.R., Everett, S.M., 2011. Review article: methods of measuring gastric acid secretion. *Aliment. Pharmacol. Ther.* 33, 768–781.
- Glicksman, C., Pournaras, D.J., Wright, M., Roberts, R., Mahon, D., Welbourn, R., Sherwood, R., Alagband-Zadeh, J., le Roux, C.W., 2010. Postprandial plasma bile acid responses in normal weight and obese subjects. *Ann. Clin. Biochem.* 47, 482–484.
- Goh, L.-H., Mohd Said, R., Go, K.-L., 2018. Lactase deficiency and lactose intolerance in a multiethnic Asian population in Malaysia. *JGH Open* 6 (2), 307–310.
- Gonçalves, P., Martel, F., 2016. Regulation of colonic epithelial butyrate transport: Focus on colorectal cancer. *Porto Biomed. J.* 1, 83–89. <https://doi.org/10.1016/j.pbj.2016.04.004>.
- Gotanda, Y., Akagi, Y., Kawahara, A., Kinugasa, T., Yoshida, T., Ryu, Y., Shiratsuchi, I., Kage, M., Shirouzu, K., 2013. Expression of monocarboxylate transporter (MCT)-4 in colorectal cancer and its role: MCT4 contributes to the growth of colorectal cancer with vascular endothelial growth factor. *Anticancer Res* 33, 2941–2947.
- Gotch, F., Nadell, J., Edelman, I.S., 1957. Gastrointestinal water and electrolytes. IV. The equilibration of deuterium oxide (D₂O) in gastrointestinal contents and the proportion of total body water (T.B.W.) in the gastrointestinal tract. *J. Clin. Invest* 36, 289–296.
- Grasso, C., Jansen, G., Giovannetti, E., 2017. Drug resistance in pancreatic cancer: Impact

- of altered energy metabolism. *Crit. Rev. Oncol. Hematol.* 114, 139–152.
- Greenblatt, D.J., Harmatz, J.S., Chow, C.R., 2018. Vortioxetine disposition in obesity: potential implications for patient safety. *J. Clin. Psychopharmacol.* 38, 172–179.
- Grimm, M., Koziol, M., Kuhn, J.P., Weitschies, W., 2018. Interindividual and intraindividual variability of fasted state gastric fluid volume and gastric emptying of water. *Eur. J. Pharm. Biopharm.* 127, 309–317.
- Grimsrud, K.N., Sherwin, C.M.T., Constance, J.E., Tak, C., Zuppa, A.F., Spigarelli, M.G., Mihalopoulos, N.L., 2015. Special population considerations and regulatory affairs for clinical research. *Clin. Res. Regul. Aff.* 32, 47–56.
- Groer, C., Busch, D., Patrzyk, M., Beyer, K., Busemann, A., Heidecke, C.D., Drozdziak, M., Siegmund, W., Oswald, S., 2014. Absolute protein quantification of clinically relevant cytochrome P450 enzymes and UDP-glucuronosyltransferases by mass spectrometry-based targeted proteomics. *J. Pharm. Biomed. Anal.* 100, 393–401.
- Grover, Z., De Nardi, A., Lewindon, P.J., 2017. Inflammatory bowel disease in adolescents. *Aust. Fam. Physician* 46, 565–571.
- Guimaraes, M., Stalelova, M., Holm, R., Reppas, C., Symillides, M., Vertzoni, M., Fotaki, N., 2019. Biopharmaceutical considerations in paediatrics with a view to the evaluation of orally administered drug products - a PEARL review. *J. Pharm. Pharmacol.* 71 (4), 603–642.
- Gulbake, A., Jain, A., Jain, A., Jain, A., Jain, S.K., 2016. Insight to drug delivery aspects for colorectal cancer. *World J. Gastroenterol.* 22, 582–599.
- Gutmann, H., Hruz, P., Zimmermann, C., Beglinger, C., Drewe, J., 2005. Distribution of breast cancer resistance protein (BCRP/ABCG2) mRNA expression along the human GI tract. *Biochem. Pharmacol.* 70 (5), 695–699.
- Gurumurthy, P., Ramachandran, G., Hemanth Kumar, A.K., Rajasekaran, S., Padmapriyadarshini, C., Swaminathan, S., Bhagavathy, S., Venkatesan, P., Sekar, L., Mahilmaran, A., Ravichandran, N., Paramesh, P., 2004. Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. *Antimicrob. Agents Chemother.* 48, 4473–4475.
- Hanley, M.J., Abernethy, D.R., Greenblatt, D.J., 2010. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin. Pharmacokinet.* 49, 71–87.
- Haro, C., Rangel-Zuniga, O.A., Alcalá-Díaz, J.F., Gomez-Delgado, F., Perez-Martinez, P., Delgado-Lista, J., Quintana-Navarro, G.M., Landa, B.B., Navas-Cortes, J.A., Tena-Sempere, M., Clemente, J.C., Lopez-Miranda, J., Perez-Jimenez, F., Camargo, A., 2016. Intestinal microbiota is influenced by gender and body mass index. *PLoS One* 11 (5), e0154090.
- Hartmanshenn, C., Scherholz, M., Androulakis, I.P., 2016. Physiologically-based pharmacokinetic models: approaches for enabling personalized medicine. *J. Pharmacokinet. Phar.* 43, 481–504.
- Haskell, H., Andrews Jr., C.W., Reddy, S.I., Dendrinos, K., Farraye, F.A., Stucchi, A.F., Becker, J.M., Odze, R.D., 2005. Pathologic features and clinical significance of "backwash" ileitis in ulcerative colitis. *Am. J. Surg. Pathol.* 29, 1472–1481.
- Hasler, W.L., Coleski, R., Chey, W.D., Koch, K.L., McCallum, R.W., Wo, J.M., Kuo, B., Sitrin, M.D., Katz, L.A., Hwang, J., Semler, J.R., Parkman, H.P., 2008. Differences in intragastric pH in diabetic vs. idiopathic gastroparesis: relation to degree of gastric retention. *Am. J. Physiol. Gastrointest. Liver Physiol.* 294, G1384–G1391.
- Hatton, G.B., Madla, C.M., Rabbie, S.C., Basit, A.W., 2018. All disease begins in the gut: Influence of gastrointestinal disorders and surgery on oral drug performance. *Int. J. Pharm.* 548, 408–422.
- Hatton, G.B., Madla, C.M., Rabbie, S.C., Basit, A.W., 2019. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption. *Drug Discov. Today* 24, 417–427.
- Hebert, M.F., Easterling, T.R., Kirby, B., Carr, D.B., Buchanan, M.L., Rutherford, T., Thummel, K.E., Fishbein, D.P., Unadkat, J.D., 2008. Effects of pregnancy on CYP3A and P-glycoprotein activities as measured by disposition of midazolam and digoxin: a University of Washington specialized center of research study. *Clin. Pharmacol. Ther.* 84, 248–253.
- Hebert, M.F., Ma, X., Narahariseti, S.B., Krudys, K.M., Umans, J.G., Hankins, G.D., Caritis, S.N., Miodovnik, M., Mattison, D.R., Unadkat, J.D., Kelly, E.J., Blough, D., Cobelli, C., Ahmed, M.S., Snodgrass, W.R., Carr, D.B., Easterling, T.R., Vicini, P., for the Obstetric-Fetal Pharmacology Research Unit Network, 2009. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. *Clin. Pharmacol. Ther.* 85, 607–614.
- Heikkinen, T., Ekblad, U., Palo, P., Laine, K., 2003. Pharmacokinetics of fluoxetine and norfluoxetine in pregnancy and lactation. *Clin. Pharmacol. Ther.* 73, 330–337.
- Hendrickson, B.A., Gokhale, R., Cho, J.H., 2002. Clinical aspects and pathophysiology of inflammatory bowel disease. *Clin. Microbiol. Rev.* 15, 79–94.
- Heyes, N., Kapoor, P., Kerr, I.D., 2018. Polymorphisms of the multidrug pump ABCG2: A systematic review of their effect on protein expression, function, and drug pharmacokinetics. *Drug Metab. Dispos.* 46, 1886–1899.
- Heyman, M., Abed, J., Lebreton, C., Cerf-Bensussan, N., 2012. Intestinal permeability in coeliac disease: insight into mechanisms and relevance to pathogenesis. *Gut* 61, 1355–1364.
- Higgs, R.H., Ellis-Pegler, R.B., Lambert, H.P., 1975. Assessment of simple methods of measuring intestinal transit times in children with gastroenteritis. *Gut* 16, 458–461.
- Hlavata, I., Mohelnikova-Duchonova, B., Vavlikova, R., Liska, V., Pitule, P., Novak, P., Bruha, J., Vycital, O., Holubec, L., Treska, V., Vodicka, P., Soucek, P., 2012. The role of ABC transporters in progression and clinical outcome of colorectal cancer. *Mutagenesis* 27, 187–196.
- Hochleitner, B., Bösmüller, C., Nehoda, H., Steurer, W., Königsrainer, A., Margreiter, R., Frühwirth, M., Simma, B., Ellemunter, H., Hochleitner, E., 2001. Increased tacrolimus levels during diarrhea. *Transpl. Int.* 14, 230–233.
- Holt, P.R., 2018. Effects of aging upon intestinal absorption. In: Moment, G.B., Adelman, R.C., Roth, G.S. (Eds.), *Nutritional Approaches to Aging Research*, first ed. CRC Press, Boca Raton, pp. 151–170.
- Horowitz, M., Cook, D.J., Collins, P.J., Harding, P.E., Hooper, M.J., Walsh, J.F., Shearman, D.J., 1982. Measurement of gastric emptying after gastric bypass surgery using radionuclides. *Br. J. Surg.* 69, 655–657.
- Hsueh, C.H., Hsu, V., Zhao, P., Zhang, L., Giacomini, K.M., Huang, S.M., 2018. PBPK modeling of the effect of reduced kidney function on the pharmacokinetics of drugs excreted renally by organic anion transporters. *Clin. Pharmacol. Ther.* 103, 485–492.
- Hu, T., Li, Z., Gao, C.Y., Cho, C.H., 2016. Mechanisms of drug resistance in colon cancer and its therapeutic strategies. *World J. Gastroenterol.* 22, 6876–6889.
- Hughes, C.A., Tseng, A., Cooper, R., 2015. Managing drug interactions in HIV-infected adults with comorbid illness. *CMAJ* 187, 36–43.
- Hultman, B., Mahteme, H., Sundbom, M., Ljungman, M., Larsson, R., Nygren, P., 2014. Benchmarking of gastric cancer sensitivity to anti-cancer drugs ex vivo as a basis for drug selection in systemic and intraperitoneal therapy. *J. Exp. Clin. Cancer Res.* 33, 110.
- Human Microbiome Project Consortium, 2012. Structure, function and diversity of the healthy human microbiome. *Nature* 486, 207–214.
- ICH, 1993. ICH harmonised tripartite guideline E7: Studies in support of special populations: Geriatrics. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Step4/E7_Guideline.pdf (accessed 11 September 2019).
- ICH, 1997. ICH harmonised tripartite guideline E8: General considerations for clinical trials. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf (accessed 11 September 2019).
- ICH, 1998. ICH harmonised tripartite guideline: Ethnic factors in the acceptability of foreign clinical data E5(R1). https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E5_R1/Step4/E5_R1_Guideline.pdf (accessed 11 September 2019).
- ICH, 2000. ICH clinical investigation of medicinal products in the pediatric population E11. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf.
- ICH, 2008. Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. https://www.ema.europa.eu/documents/scientific-guideline/ich-m-3-r-2-non-clinical-safety-studies-conduct-human-clinical-trials-marketing-authorization_en.pdf (accessed 11 September 2019).
- Irving, A.B., Wood, C.G., Bennotti, N.P., Babu, E., Deshpande, A., Lent, R.M., Petrick, A., Gabrielsen, J., Strodel, W., Gerhard, S.G., Still, D.C., Ganapathy, V., Rolston, D.D., 2016. Nutrient transporter expression in the jejunum in relation to body mass index in patients undergoing bariatric surgery. *Nutrients* 8 (11), 683.
- Jackson, S.J., Leahy, F.E., McGowan, A.A., Bluck, L.J.C., Coward, W.A., Jebb, S.A., 2004. Delayed gastric emptying in the obese: an assessment using the non-invasive 13C-octanoic acid breath test. *Diabetes Obes. Metabol.* 6, 264–270.
- Jamei, M., Turner, D., Yang, J., Neuhoof, S., Polak, S., Rostami-Hodjegan, A., Tucker, G., 2009. Population-based mechanistic prediction of oral drug absorption. *AAPS J* 11, 225–237.
- Johnson, J.A., 1997. Influence of race or ethnicity on pharmacokinetics of drugs. *J. Pharm. Sci.* 86, 1328–1333.
- Johnson, T.N., Bonner, J.J., Tucker, G.T., Turner, D.B., Jamei, M., 2018. Development and applications of a physiologically-based model of paediatric oral drug absorption. *Eur. J. Pharm. Sci.* 115, 57–67.
- Johnson, T.N., Tanner, M.S., Taylor, C.J., Tucker, G.T., 2001. Enterocytic CYP3A4 in a paediatric population: developmental changes and the effect of coeliac disease and cystic fibrosis. *Br. J. Clin. Pharmacol.* 51, 451–460.
- Jones, H.M., Chen, Y., Gibson, C., Heimbach, T., Parrott, N., Peters, S.A., Snoeys, J., Upreti, V.V., Zheng, M., Hall, S.D., 2015. Physiologically based pharmacokinetic modeling in drug discovery and development: a pharmaceutical industry perspective. *Clin. Pharmacol. Ther.* 97, 247–262.
- Joshi, G., Kumar, A., Sawant, K., 2014. Enhanced bioavailability and intestinal uptake of Gemcitabine HCl loaded PLGA nanoparticles after oral delivery. *Eur. J. Pharm. Sci.* 60, 80–89.
- Jost, W.H., 2010. Gastrointestinal dysfunction in Parkinson's Disease. *J. Neurol. Sci.* 289, 69–73. <https://doi.org/10.1016/j.jns.2009.08.020>.
- Juvin, P., Fèvre, G., Merouche, M., Vallot, T., Desmonts, J.M., 2001. Gastric residue is not more copious in obese patients. *Anesth. Analg.* 93, 1621–1622.
- Kang, H., Kim, I., Park, J., Shin, Y., Ku, J., Jung, M., Yoo, B., Kim, H., Park, J., 2004. Identification of genes with differential expression in acquired drug-resistant gastric cancer cells using high-density oligonucleotide microarrays. *Clin. Cancer Res.* 10, 272–284.
- Kar, P., Jones, K.L., Horowitz, M., Chapman, M.J., Deane, A.M., 2015. Measurement of gastric emptying in the critically ill. *Clin. Nutr.* 34, 557–564.
- Karkosa, F., Krueger, A., Urbaniak, J., Klein, S., 2017. Simulating different dosing scenarios for a child-appropriate valproate ER formulation in a new pediatric two-stage dissolution model. *AAPS PharmSciTech* 18, 309–316.
- Kashyap, P., Farrugia, G., 2010. Diabetic gastroparesis: what we have learned and had to unlearn in the past 5 years. *Gut* 59, 1716–1726.
- Ke, A.B., Greupink, R., Abduljalil, K., 2018. Drug dosing in pregnant women: challenges and opportunities in using physiologically based pharmacokinetic modeling and simulations. *CPT Pharmacometrics. Syst. Pharmacol.* 7, 103–110.
- Kenney, W.L., Chiu, P., 2001. Influence of age on thirst and fluid intake. *Med. Sci. Sports. Exerc.* 33, 1524–1532.
- Khan, M.S., Roberts, M.S., 2018. Challenges and innovations of drug delivery in older age. *Adv. Drug. Deliv. Rev.* 135, 3–38.
- Kim, D.H., Yun, H.Y., Song, Y.-J., Ryu, D.H., Han, H.-S., Han, J.-H., Kim, K.B., Yoon, S.M., Yoon, S.J., 2017. Clinical features of gastric emptying after distal gastrectomy. *Ann. Surg. Treat. Res.* 93, 310–315.
- Kim, J.S., Sung, H.Y., 2015. Gastrointestinal autonomic dysfunction in patients with Parkinson's Disease. *J. Mov. Disord.* 8, 76–82.
- Kim, M.K., Osada, T., Barry, W.T., Yang, X.Y., Freedman, J.A., Tsamis, K.A., Datto, M., Clary, B.M., Clay, T., Morse, M.A., Febbo, P.G., Lyerly, H.K., Hsu, D.S., 2012.

- Characterization of an oxalipatin sensitivity predictor in a preclinical murine model of colorectal cancer. *Mol. Cancer Ther.* 11, 1500–1509.
- Kitis, G., Lucas, M.L., Bishop, H., Sargent, A., Schneider, R.E., Blair, J.A., Allan, R.N., 1982. Altered jejunal surface pH in coeliac disease: its effect on propranolol and folic acid absorption. *Clin. Sci. (London)* 63, 373–380.
- Klingmann, V., Linderskamp, H., Meissner, T., Mayatepek, E., Moeltner, A., Breikreutz, J., Bosse, H.M., 2018. Acceptability of multiple uncoated minitables in infants and toddlers: A randomized controlled trial. *J. Pediatr.* 201, 202–207 e201.
- Knutti, R., Rothweiler, H., Schlatter, C., 1981. Effect of pregnancy on the pharmacokinetics of caffeine. *Eur. J. Clin. Pharmacol.* 21, 121–126.
- Kodidela, S., Kumar, S.S., Uppugunduri, C.R.S., 2017. Developmental pattern of hepatic drug-metabolizing enzymes in pediatric population and its role in optimal drug treatment. *Arch. Med. Health Sci.* 5 (1), 115–122.
- Kohlmann, P., Stillhart, C., Kuentz, M., Parrott, N., 2017. Investigating oral absorption of carbamazepine in pediatric populations. *AAPS J* 19, 1864–1877.
- Kostewicz, E.S., Aarons, L., Bergstrand, M., Bolger, M.B., Galetin, A., Hatley, O., Jamei, M., Lloyd, R., Pepin, X., Rostami-Hodjegan, A., Sjogren, E., Tannergren, C., Turner, D.B., Wagner, C., Weitschies, W., Dressman, J., 2014. PBPK models for the prediction of in vivo performance of oral dosage forms. *Eur. J. Pharm. Sci.* 57, 300–321.
- Koziolek, M., Grimm, M., Becker, D., Iordanov, V., Zou, H., Shimizu, J., Wanke, C., Garbacz, G., Weitschies, W., 2015. Investigation of pH and temperature profiles in the GI tract of fasted human subjects using the Intellipac(RR) system. *J. Pharm. Sci.* 104, 2855–2863.
- Koziolek, M., Grimm, M., Garbacz, G., Kuhn, J.P., Weitschies, W., 2014. Intra gastric volume changes after intake of a high-caloric, high-fat standard breakfast in healthy human subjects investigated by MRI. *Mol. Pharm.* 11, 1632–1639.
- Krecic-Shepard, M.E., Barnas, C., Slimko, J., Jones, M., Schwartz, J.B., 2000. Gender-specific effects on verapamil pharmacokinetics and pharmacodynamics in humans. *J. Clin. Pharmacol.* 40, 219–230.
- Kuehl, C.J., Wood, H.D., Marsh, T.L., Schmidt, T.M., Young, V.B., 2005. Colonization of the cecal mucosa by *Helicobacter hepaticus* impacts the diversity of the indigenous microbiota. *Infect. Immun.* 73, 6952–6961.
- Kuitunen, M., Savilahti, E., 1996. Gut permeability to human alpha-lactalbumin, beta-lactoglobulin, mannitol, and lactulose in celiac disease. *J. Pediatr. Gastroenterol. Nutr.* 22, 197–204.
- Kumagai, T., Nagayama, H., Ota, T., Nishiyama, Y., Mishina, M., Ueda, M., 2014. Sex differences in the pharmacokinetics of levodopa in elderly patients with Parkinson Disease. *Clin. Neuropharmacol.* 37, 173–176.
- Kumar, R., Lieske, J.C., Collazo-Clavell, M.L., Sarr, M.G., Olson, E.R., Vrtiska, T.J., Bergstralh, E.J., Li, X., 2011. Fat malabsorption and increased intestinal oxalate absorption are common after Roux-en-Y gastric bypass surgery. *Surgery* 149, 654–661.
- Kumar, S., Tana, A., Shankar, A., 2014. Cystic fibrosis - What are the prospects for a cure? *Eur. J. Int. Med* 25, 803–807.
- Kuribayashi, R., Takishita, T., Mikami, K., 2016. Regulatory considerations of bioequivalence studies for oral solid dosage forms in Japan. *J. Pharm. Sci.* 105 (8), 2270–2277.
- Lahner, E., Annibale, B., Della Fave, G., 2009. Systematic review: *Helicobacter pylori* infection and impaired drug absorption. *Aliment. Pharmacol. Ther.* 29, 379–386.
- Lahner, E., Virili, C., Santaguida, M.G., Annibale, B., Centanni, M., 2014. *Helicobacter pylori* infection and drugs malabsorption. *World J. Gastroenterol.* 20, 10331–10337.
- Lang, C.C., Brown, R.M., Kinirons, M.T., Deathridge, M.A., Guengerich, F.P., Kelleher, D., O'Brian, D.S., Ghishan, F.K., Wood, A.J., 1996. Decreased intestinal CYP3A in celiac disease: reversal after successful gluten-free diet: a potential source of interindividual variability in first-pass drug metabolism. *Clin. Pharmacol. Ther.* 59, 41–46.
- Lebwohl, B., Sanders, D.S., Green, P.H.R., 2018. Coeliac disease. *Lancet* 391, 70–81.
- Lee, J.Y., Lee, I., Chang, W.J., Ahn, S.M., Lim, S.H., Kim, H.S., Yoo, K.H., Jung, K.S., Song, H.N., Cho, J.H., Kim, S.Y., Kim, K.M., Lee, S., Kim, S.T., Park, S.H., Lee, J., Park, J.O., Park, Y.S., Lim, H.Y., Kang, W.K., 2016. MCT4 as a potential therapeutic target for metastatic gastric cancer with peritoneal carcinomatosis. *Oncotarget* 7, 43492–43503.
- Leke, A.Z., Dolk, H., Loane, M., Casson, K., Maboh, N.M., Maeya, S.E., Ndumbe, L.D., Nyenti, P.B., Armstrong, O., Etiendem, D., 2018. First trimester medication use in pregnancy in Cameroon: a multi-hospital survey. *BMC Pregnancy Childb* 18, 450.
- Li, H., He, J., Jia, W., 2016. The influence of gut microbiota on drug metabolism and toxicity. *Expert Opin. Drug Metab. Toxicol.* 12, 31–40.
- Li, R., Barton, H.A., 2018. Explaining ethnic variability of transporter substrate pharmacokinetics in healthy Asian and Caucasian subjects with allele frequencies of OATP1B1 and BCRP: A mechanistic modeling analysis. *Clin. Pharmacokinet.* 57, 491–503.
- Lim, S.G., Lipman, M.C., Squire, S., Pillay, D., Gillespie, S., Sankey, E.A., Dhillon, A.P., Johnson, M.A., Lee, C.A., Pounder, R.E., 1993. Audit of endoscopic surveillance biopsy specimens in HIV positive patients with gastrointestinal symptoms. *Gut* 34, 1429–1432.
- Lin, C., Ng, H.L., Pan, W., Chen, H., Zhang, G., Bian, Z., Lu, A., Yang, Z., 2015. Exploring different strategies for efficient delivery of colorectal cancer therapy. *Int. J. Mol. Sci.* 16, 26936–26952.
- Linnebjerg, H., Park, S., Kothare, P.A., Trautmann, M.E., Mace, K., Fineman, M., Wilding, I., Nauck, M., Horowitz, M., 2008. Effect of exenatide on gastric emptying and relation to postprandial glycemia in type 2 diabetes. *Regul. Pept.* 151, 123–129.
- Lozoya-Agullo, I., Gonzalez-Alvarez, I., Gonzalez-Alvarez, M., Merino-Sanjuan, M., Bermejo, M., 2015. In situ perfusion model in rat colon for drug absorption studies: Comparison with small intestine and Caco-2 cell model. *J. Pharm. Sci.* 104, 3136–3145.
- Lu, P.-J., Hsu, P.-I., Chen, C.-H., Hsiao, M., Chang, W.-C., Tseng, H.-H., Lin, K.-H., Chuah, S.-K., Chen, H.-C., 2010. Gastric juice acidity in upper gastrointestinal diseases. *World J. Gastroenterol.* 16, 5496–5501.
- Ludvigsson, J.F., Card, T.R., Kaukinen, K., Bai, J., Zingone, F., Sanders, D.S., Murray, J.A., 2015. Screening for celiac disease in the general population and in high-risk groups. *United European Gastroenterol. J.* 3, 106–120.
- Ma, X., Wang, H., Zhang, P., Xu, L., Tian, Z., 2019. Association between small intestinal bacterial overgrowth and toll-like receptor 4 in patients with pancreatic carcinoma and cholangiocarcinoma. *Turk. J. Gastroenterol.* 30, 177–183.
- Mahajan, P., Hashmi, J., Singh, R., Samra, T., Aneja, S., 2015. Comparative evaluation of gastric pH and volume in morbidly obese and lean patients undergoing elective surgery and effect of aspiration prophylaxis. *J. Clin. Anesth.* 27, 396–400.
- Maharaj, A.R., Edginton, A.N., Fotaki, N., 2016. Assessment of age-related changes in pediatric gastrointestinal solubility. *Pharm. Res.* 33, 52–71.
- Maharaj, A.R., Edginton, A.N., 2016. Examining small intestinal transit time as a function of age: is there evidence to support age-dependent differences among children? *Drug Metab. Dispos* 44 (7), 1080–1089.
- Mai, Y., Afonso-Pereira, F., Murdan, S., Basit, A.W., 2017. Excipient-mediated alteration in drug bioavailability in the rat depends on the sex of the animal. *Eur. J. Pharm. Sci.* 107, 249–255.
- Mai, Y., Dou, L., Madla, C.M., Murdan, S., Basit, A.W., 2019. Sex-dependence in the effect of pharmaceutical excipients: polyoxyethylated solubilising excipients increase oral drug bioavailability in male but not female rats. *Pharmaceutics* 11.
- Mai, Y., Dou, L., Murdan, S., Basit, A.W., 2018a. An animal's sex influences the effects of the excipient PEG 400 on the intestinal P-gp protein and mRNA levels, which has implications for oral drug absorption. *Eur. J. Pharm. Sci.* 120, 53–60.
- Mai, Y., Murdan, S., Awadi, M., Basit, A.W., 2018b. Establishing an in vitro permeation model to predict the in vivo sex-related influence of PEG 400 on oral drug absorption. *Int. J. Pharm.* 542 (1–2), 280–287.
- Malebranche, R., Arnoux, E., Guerin, J.M., Pierre, G.D., Laroche, A.C., Pean-Guichard, C., Elie, R., Morisset, P.H., Spira, T., Mandeville, R., et al., 1983. Acquired immunodeficiency syndrome with severe gastrointestinal manifestations in Haiti. *Lancet* 2, 873–878.
- Marathe, C.S., Rayner, C.K., Jones, K.L., Horowitz, M., 2013. Relationships between gastric emptying, postprandial glycemia, and incretin hormones. *Diabetes Care* 36, 1396–1405.
- Matsuoka, H., Maeda, K., Katsuno, H., Tsunoda, A., Koda, K., Ohge, H., Oya, M., Yoshioka, K., Imazu, Y., Masaki, T., 2011. Recovery of upper gastrointestinal bowel movement after rectosigmoid cancer surgery: a pilot transit analysis. *Int. Surgery* 96, 281–285.
- McCreight, L.J., Bailey, C.J., Pearson, E.R., 2016. Metformin and the gastrointestinal tract. *Diabetologia* 59, 426–435.
- McDougall, C.J., Wong, R., Scudera, P., Lesser, M., DeCossé, J.J., 1993. Colonic mucosal pH in humans. *Digest. Dis. Sci.* 38, 542–545.
- McEwen, B.S., 2014. Sex, stress and the brain: interactive actions of hormones on the developing and adult brain. *17(2)*, 18–25.
- McGready, R., Stepniowska, K., Seaton, E., Cho, T., Cho, D., Ginsberg, A., Edstein, M.D., Ashley, E., Looaresuwan, S., White, N.J., Nosten, F., 2003. Pregnancy and use of oral contraceptives reduces the biotransformation of proguanil to cycloguanil. *Eur. J. Clin. Pharmacol.* 59, 553–557.
- McGregor, A.J., Markowitz, J.S., Forrester, J., Shader, R.L., 2017. Joining the effort: the challenges in establishing guidelines for sex- and gender-specific research design in clinical therapeutic studies. *Clin. Ther.* 39, 1912–1916.
- McIlleron, H., Rustomjee, R., Vahedi, M., Mthiyane, T., Denti, P., Connolly, C., Rida, W., Pym, A., Smith, P.J., Onyebujoh, P.C., 2012. Reduced antituberculosis drug concentrations in HIV-infected patients who are men or have low weight: implications for international dosing guidelines. *Antimicrob. Agents Chemother.* 56, 3232–3238.
- McKinley, M.J., Denton, D.A., Thomas, C.J., Woods, R.L., Mathai, M.L., 2006. Differential effects of aging on fluid intake in response to hypovolemia, hypertonicity, and hormonal stimuli in Munich Wistar rats. *Proc. Natl. Acad. Sci.* 103, 3450–3455.
- Mearin, F., de Ribot, X., Balboa, A., Salas, A., Varas, M.J., Cudala, M., Bartolomé, R., Armengol, J.R., Malagelada, J.R., 1995. Does *Helicobacter pylori* infection increase gastric sensitivity in functional dyspepsia? *Gut* 37, 47–51.
- Mehandru, S., Poles, M.A., Tenner-Racz, K., Horowitz, A., Hothery, A., Hogan, C., Boden, D., Racz, P., Markowitz, M., 2004. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J. Exp. Med.* 200, 761–770.
- Metcalf, A.M., Phillips, S.F., Zinsmeister, A.R., MacCarty, R.L., Beart, R.W., Wolff, B.G., 1987. Simplified assessment of segmental colonic transit. *Gastroenterology* 92, 40–47.
- Michielan, A., D'Inca, R., 2015. Intestinal permeability in inflammatory bowel disease: pathogenesis, clinical evaluation, and therapy of leaky gut. *Mediat. Inflamm.* 2015, 628157.
- Miller, A.D., Smith, K.M., 2006. Medication and nutrient administration considerations after bariatric surgery. *Am. J. Health-Syst. Pharm.* 63, 1852–1857.
- Miyaji, H., Azuma, T., Ito, S., Abe, Y., Ono, H., Suto, H., Ito, Y., Yamazaki, Y., Kohli, Y., Kuriyama, M., 1999. The effect of *Helicobacter pylori* eradication therapy on gastric antral myoelectrical activity and gastric emptying in patients with non-ulcer dyspepsia. *Aliment. Pharmacol. Ther.* 13, 1473–1480.
- Miyauchi, E., Tachikawa, M., Declèves, X., Uchida, Y., Bouillot, J.-L., Poitou, C., Oppert, J.-M., Mouly, S., Bergmann, J.-F., Terasaki, T., Scherrmann, J.-M., Lloret-Linares, C., 2016. Quantitative atlas of cytochrome P450, UDP-glucuronosyltransferase, and transporter proteins in jejunum of morbidly obese subjects. *Mol. Pharm.* 13, 2631–2640.
- Mojaverian, P., Vlases, P.H., Kellner, P.E., Rocci Jr., M.L., 1988. Effects of gender, posture, and age on gastric residence time of an indigestible solid: pharmaceutical considerations. *Pharm. Res.* 5, 639–644.
- Mooij, M.G., de Koning, B.A., Huijsman, M.L., de Wildt, S.N., 2012. Ontogeny of oral drug absorption processes in children. *Expert Opin. Drug Metab. Toxicol.* 8, 1293–1303.

- Mooij, M.G., De Koning, B.E.A., Lindenberg-Kortleve, D.J., Simons-Oosterhuis, Y., Van Groen, B.D., Tibboel, D., Samsom, J.N., De Wildt, S.N., 2016a. Human intestinal PEPT1 transporter expression and localization in preterm and term infants. *Drug Metab. Dispos.* 44, 1014–1019.
- Mooij, M.G., Nies, A.T., Knibbe, C.A.J., Schaeffeler, E., Tibboel, D., Schwab, M., de Wildt, S.N., 2016b. Development of human membrane transporters: drug disposition and pharmacogenetics. *Clin. Pharmacokinet.* 55, 507–524.
- Mooij, M.G., Van De Steeg, E., Van Rosmalen, J., Windster, J.D., De Koning, B.A.E., Vaes, W.H.J., Van Groen, B.D., Tibboel, D., Wortelboer, H.M., De Wildt, S.N., 2016c. Proteomic analysis of the developmental trajectory of human hepatic membrane transporter proteins in the first three months of life. *Drug Metab. Dispos.* 44, 1005–1013.
- Moringo, R., Moize, V., Musri, M., Lacy, A.M., Navarro, S., Marin, J.L., Delgado, S., Casamitjana, R., Vidal, J., 2006. Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. *J. Clin. Endocrinol. Metab.* 91, 1735–1740.
- Mouly, S., Lloret-Linares, C., Sellier, P.O., Sene, D., Bergmann, J.F., 2017. Is the clinical relevance of drug-food and drug-herb interactions limited to grapefruit juice and Saint-John's Wort? *Pharmacol. Res.* 118, 82–92.
- Mourad, F.H., Barada, K.A., Saade, N.E., 2017. Impairment of small intestinal function in ulcerative colitis: role of enteric innervation. *J. Crohns Colitis* 11, 369–377.
- Mudie, D.M., Murray, K., Hoad, C.L., Pritchard, S.E., Garnett, M.C., Amidon, G.L., Gowland, P.A., Spiller, R.C., Amidon, G.E., Marciani, L., 2014. Quantification of gastrointestinal liquid volumes and distribution following a 240 mL dose of water in the fasted state. *Mol. Pharm.* 11, 3039–3047.
- Mullertz, A., Fatouros, D.G., Vertzoni, M., Reppas, C., 2013. Unravelling the ultra-structure of ascending colon fluids from patients with ulcerative colitis by cryogenic transmission electron microscopy. *J. Pharm. Pharmacol.* 65, 1482–1487.
- Munoz-Torres, M., Varsavsky, M., Alonso, G., 2006. Lactose intolerance revealed by severe resistance to treatment with levothyroxine. *Thyroid* 16, 1171–1173.
- Murray, K., Hoad, C.L., Mudie, D.M., Wright, J., Heissam, K., Abrehart, N., Pritchard, S.E., Al Atwah, S., Gowland, P.A., Amidon, G.E., Garnett, M.C., Amidon, G.E., Spiller, R.C., Amidon, G.L., Marciani, L., 2017. Magnetic resonance imaging quantification of fasted state colonic liquid pockets in healthy humans. *Mol. Pharm.* 14 (8), 2629–2638.
- Mustalhti, K., Catassi, C., Reunanen, A., Fabiani, E., Heier, M., McMillan, S., Murray, L., Metzger, M.H., Gasparin, M., Bravi, E., Maki, M., 2010. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann. Med.* 42, 587–595.
- Näslund, I., Beckman, K.W., 1987. Gastric emptying rate after gastric bypass and gastropasty. *Scand. J. Gastroenterol.* 22, 193–201.
- Neal-Kluever, A., Fisher, J., Grylack, L., Kakiuchi-Kiyota, S., Halpern, W., 2019. Physiology of the neonatal gastrointestinal system relevant to the disposition of orally administered medications. *Drug Metab. Dispos.* 47 (3), 296–313.
- Neff, K.J., Le Roux, C.W., 2014. Bariatric surgery: the indications in metabolic disease. *Digest. Surg.* 31, 6–12.
- Neff, K.J., Olbers, T., Le Roux, C.W., 2013. Bariatric surgery: the challenges with candidate selection, individualizing treatment and clinical outcomes. *BMC Medicine* 11, 8.
- Nelson John, D., Shelton, S., Kusmiesz Helen, T., Haltalin Kenneth, C., 1972. Absorption of ampicillin and nalidixic acid by infants and children with acute shigellosis. *Clin. Pharmacol. Therap.* 13, 879–886.
- Niwa, T., Yamamoto, S., Saito, M., Shiraga, T., Takagi, A., 2007. Effect of cyclosporine and tacrolimus on cytochrome p450 activities in human liver microsomes. *Yakugaku Zasshi* 127 (1), 209–216.
- Norman, J.L., Fixen, D.R., Saseen, J.J., Saba, L.M., Linnebur, S.A., 2017. Zolpidem prescribing practices before and after Food and Drug Administration required product labeling changes. *SAGE Open Med* 5, 2050312117707687.
- Nugent, S.G., Kumar, D., Rampton, D.S., Evans, D.F., 2001. Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosaliclates and other drugs. *Gut* 48, 571–577.
- O'Sullivan, G.M., Bullingham, R.E., 1984. The assessment of gastric acidity and antacid effect in pregnant women by a non-invasive radiotelemetry technique. *Br. J. Obstet. Gynaecol.* 91, 973–978.
- Oami, T., Hattori, N., Matsumura, Y., Watanabe, E., Abe, R., Oshima, T., Takahashi, W., Yamazaki, S., Suzuki, T., Oda, S., 2017. The effects of fasting and massive diarrhea on absorption of enteral vancomycin in critically ill patients: A retrospective observational study. *Front. Med.* 4, 70.
- Obuchi, W., Ohtsuki, S., Uchida, Y., Ohmine, K., Yamori, T., Terasaki, T., 2013. Identification of transporters associated with Etoposide sensitivity of stomach cancer cell lines and methotrexate sensitivity of breast cancer cell lines by quantitative targeted absolute proteomics. *Mol. Pharmacol.* 83, 490–500.
- Odstreil, E.A., Martinez, J.G., Santa Ana, C.A., Xue, B., Schneider, R.E., Steffer, K.J., Porter, J.L., Asplin, J., Kuhn, J.A., Fordtran, J.S., 2010. The contribution of malabsorption to the reduction in net energy absorption after long-limb Roux-en-Y gastric bypass. *Am. J. Clin. Nutr.* 92, 704–713.
- Ohman, I., Beck, O., Vitols, S., Tomson, T., 2008. Plasma concentrations of lamotrigine and its 2-N-glucuronide metabolite during pregnancy in women with epilepsy. *Epilepsia* 49, 1075–1080.
- Olesen, A.E., Brokjaer, A., Fisher, I.W., Larsen, L.M., 2013. Pharmacological challenges in chronic pancreatitis. *World J. Gastroenterol.* 19, 7302–7307.
- Orditura, M., Galizia, G., Sforza, V., Gambardella, V., Fabozzi, A., Laterza, M.M., Andreozzi, F., Ventriglia, J., Savastano, B., Mabilia, A., Lieto, E., Ciardiello, F., De Vita, F., 2014. Treatment of gastric cancer. *World J. Gastroenterol.* 20, 1635–1649.
- Padwal, R., Brocks, D., Sharma, A.M., 2010. A systematic review of drug absorption following bariatric surgery and its theoretical implications. *Obes. Rev.* 11, 41–50.
- Padwal, R.S., Gabr, R.Q., Sharma, A.M., Langkaas, L.A., Birch, D.W., Karmali, S., Brocks, D.R., 2011. Effect of gastric bypass surgery on the absorption and bioavailability of metformin. *Diabetes Care* 34, 1295–1300.
- Pariente, G., Leibson, T., Carls, A., Adams-Webber, T., Ito, S., Koren, G., 2016. Pregnancy-associated changes in pharmacokinetics: A systematic review. *PLoS Med* 13, e1002160.
- Park, J.Y., Mitrou, P.N., Luben, R., Khaw, K.T., Bingham, S.A., 2009. Is bowel habit linked to colorectal cancer? - Results from the EPIC-Norfolk study. *Eur. J. Cancer* 45, 139–145.
- Patti, M.E., Houten, S.M., Bianco, A.C., Bernier, R., Larsen, P.R., Holst, J.J., Badman, M.K., Maratos-Flier, E., Mun, E.C., Pihlajamaki, J., Auwerx, J., Goldfine, A.B., 2009. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. *Obesity* 17, 1671–1677.
- Perez de la Cruz Moreno, M., Oth, M., Deferme, S., Lammert, F., Tack, J., Dressman, J., Augustijns, P., 2006. Characterization of fasted-state human intestinal fluids collected from duodenum and jejunum. *J. Pharm. Pharmacol.* 58, 1079–1089.
- Perri, F., Pastore, M., Zicoella, A., Annese, V., Quitadamo, M., Andriulli, A., 2000. Gastric emptying of solids is delayed in celiac disease and normalizes after gluten withdrawal. *Acta paed* 89, 921–925.
- Peter, S., Navis, G., de Borst, M.H., von Schacky, C., van Orten-Luiten, A.C.B., Zhermakova, A., Witkamp, R.F., Janse, A., Weber, P., Bakker, S.J.L., Eggersdorfer, M., 2017. Public health relevance of drug-nutrition interactions. *Eur. J. Nutr.* 56, 23–36.
- Peters, S.A., Jones, C.R., Ungell, A.L., Hatley, O.J., 2016. Predicting drug extraction in the human gut wall: Assessing contributions from drug metabolizing enzymes and transporter proteins using preclinical models. *Clin. Pharmacokinet.* 55, 673–696.
- Petrini, E., Caviglia, G.P., Pellicano, R., Saracco, G.M., Morino, M., Ribaldone, D.G., 2019. Risk of drug interactions and prescription appropriateness in elderly patients. *Ir. J. Med. Sci.*
- Pfeiffer, R.F., 1998. Gastrointestinal dysfunction in Parkinson's disease. *Clin. Neurosc.* 5, 136–146.
- Pfeiffer, R.F., 2011. Gastrointestinal dysfunction in Parkinson's disease. *Parkinsonism Relat. D.* 17, 10–15.
- Phan, J., Benhammou, J.N., Pisegna, J.R., 2015. Gastric hypersecretory states: investigation and management. *Curr. Treat. Options Gastroenterol.* 13 (4), 386–397.
- Pierantozzi, M., Pietrousti, A., Brusa, L., Galati, S., Stefani, A., Lunardi, G., Fedele, E., Sancesario, G., Bernardi, G., Bergamaschi, A., Magrini, A., Stanzione, P., Galante, A., 2006. Helicobacter pylori eradication and L-dopa absorption in patients with PD and motor fluctuations. *Neurology* 66, 1824–1829.
- Pierantozzi, M., Pietrousti, A., Sancesario, G., Lunardi, G., Fedele, E., Giacomini, P., Frasca, S., Galante, A., Marciani, M.G., Stanzione, P., 2001. Reduced L-dopa absorption and increased clinical fluctuations in Helicobacter pylori-infected Parkinson's disease patients. *Neurol. Sci.* 22, 89–91.
- Pinheiro, C., Longatto-Filho, A., Scapulatempo, C., Ferreira, L., Martins, S., Pellerin, L., Rodrigues, M., Alves, V.A., Schmitt, F., Baltazar, F., 2008. Increased expression of monocarboxylate transporters 1, 2, and 4 in colorectal carcinomas. *Virchows Arch.* 452, 139–146.
- Poirier, A.A., Aube, B., Cote, M., Morin, N., Di Paolo, T., Soulet, D., 2016. Gastrointestinal dysfunctions in Parkinson's disease: symptoms and treatments. *Parkinsons Dis.* 2016, 6762528.
- Poles, M.A., Elliott, J., Taing, P., Anton, P.A., Chen, I.S., 2001. A preponderance of CCR5(+) CXCR4(+) mononuclear cells enhances gastrointestinal mucosal susceptibility to human immunodeficiency virus type 1 infection. *J. Virol.* 75, 8390–8399.
- Pradhan, S., Shi, X., Hijrat, K.A., Liu, C.X., Maharjan, P., 2017. An analysis of possible risk factors contributing to delayed gastric emptying after distal gastrectomy for gastric cancer. *J. Dig. Dis.* 7.
- Pye, G., Evans, D.F., Ledingham, S., Hardcastle, J.D., 1990. Gastrointestinal intraluminal pH in normal subjects and those with colorectal adenoma or carcinoma. *Gut* 31, 1355–1357.
- Rademacher, M., 2001. Do women have more adverse drug reactions? *Am. J. Clin. Dermatol* 2, 349–351.
- Rao, S.S.C., Kuo, B., McCallum, R.W., Chey, W.D., DiBaise, J.K., Hasler, W.L., Koch, K.L., Lackner, J.M., Miller, C., Saad, R., Semler, J.R., Sitrin, M.D., Wilding, G.E., Parkman, H.P., 2009. Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation. *Clin. Gastroenterol. Hepatol.* 7 (5), 537–544.
- Rasool, M.F., Khalil, F., Laer, S., 2015. A physiologically based pharmacokinetic drug-disease model to predict carvedilol exposure in adult and paediatric heart failure patients by incorporating pathophysiological changes in hepatic and renal blood flows. *Clin. Pharmacokinet.* 54, 943–962.
- Riethorst, D., Mols, R., Duchateau, G., Tack, J., Brouwers, J., Augustijns, P., 2016. Characterization of human duodenal fluids in fasted and fed state conditions. *J. Pharm. Sci.* 105, 673–681.
- Roberts, D.J., Hall, R.I., 2013. Drug absorption, distribution, metabolism and excretion considerations in critically ill adults. *Expert Opin. Drug Metab. Toxicol.* 9, 1067–1084.
- Rosen, M.J., Dhawan, A., Saeed, S.A., 2015. Inflammatory bowel disease in children and adolescents. *JAMA Pediatrics* 169, 1053–1060.
- Rubio-Tapia, A., Murray, J.A., 2010. Celiac disease. *Curr. Opin. Gastroenterol* 26, 116–122.
- Russell, T.L., Berardi, R.R., Barnett, J.L., Dermentzoglou, L.C., Jarvenpaa, K.M., Schmaltz, S.P., Dressman, J.B., 1993. Upper gastrointestinal pH in seventy-nine healthy, elderly, North American men and women. *Pharm. Res.* 10, 187–196.
- Saint-Marcoux, F., Knoop, C., Debord, J., Thiry, P., Rousseau, A., Estenne, M., Marquet, P., 2005. Pharmacokinetic study of tacrolimus in cystic fibrosis and non-cystic fibrosis lung transplant patients and design of Bayesian estimators using limited sampling strategies. *Clin. Pharmacokinet.* 44, 1317–1328.
- Sairenji, T., Collins, K.L., Evans, D.V., 2017. An update on inflammatory bowel disease.

- Primary care 44, 673–692.
- Samant, T.S., Mangal, N., Lukacova, V., Schmidt, S., 2015. Quantitative clinical pharmacology for size and age scaling in pediatric drug development: A systematic review. *J. Clin. Pharmacol.* 55, 1207–1217.
- Samsel, A., Seneff, S., 2013. Glycosylated pathways to modern diseases II: Celiac sprue and gluten intolerance. *Interdiscip. Toxicol.* 6, 159–184.
- Santamaría, M.M., Villafranca, J.J.A., Abilés, J., López, A.F., Rodas, L.V., Goitia, B.T., Navarro, P.U., 2018. Systematic review of drug bioavailability following gastrointestinal surgery. *Eur. J. Clin. Pharmacol.* 74, 1531–1545.
- Sanz, Y., De Pama, G., Laparra, M., 2011. Unraveling the ties between celiac disease and intestinal microbiota. *Int. Rev. Immunol.* 30, 207–218.
- Sarosiek, I., Selover, K.H., Katz, L.A., Semler, J.R., Wilding, G.E., Lackner, J.M., Sitrin, M.D., Kuo, B., Chey, W.D., Hasler, W.L., Koch, K.L., Parkman, H.P., Sarosiek, J., McCallum, R.W., 2010. The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. *Aliment. Pharmacol. Ther.* 31, 313–322.
- Scarpello, J.H., Greaves, M., Sladen, G.E., 1976. Small intestinal transit in diabetics. *BMJ* 2, 1225–1226.
- Schiller, C., Frohlich, C.P., Giessmann, T., Siegmund, W., Monnikes, H., Hosten, N., Weitschies, W., 2005. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. *Aliment. Pharmacol. Ther.* 22, 971–979.
- Schiller, L., 1999. Secretory diarrhoea. *Curr. Gastroenterol. Rep* 1, 389–397.
- Schlender, J.F., Vozmediano, V., Golden, A.G., Rodríguez, M., Samant, T.S., Lagishetty, C.V., Eissing, T., Schmidt, S., 2018. Current strategies to streamline pharmacotherapy for older adults. *Eur. J. Pharm. Sci.* 111, 432–442.
- Seaman, J.S., Bowers, S.P., Dixon, P., Schindler, L., 2005. Dissolution of common psychiatric medications in a Roux-en-Y gastric bypass model. *Psychosomatics* 46, 250–253.
- Sekirov, I., Finlay, B.B., 2009. The role of the intestinal microbiota in enteric infection. *The J. Physiol.* 587, 4159–4167.
- Sharpstone, D., Neild, P., Crane, R., Taylor, C., Hodgson, C., Sherwood, R., Gazzard, B., Bjarnason, I., 1999. Small intestinal transit, absorption, and permeability in patients with AIDS with and without diarrhoea. *Gut* 45, 70–76.
- Shelton, M.J., Akbari, B., Hewitt, R.G., Adams, J.M., Morse, G.D., 2000. Eradication of *Helicobacter pylori* is associated with increased exposure to delavirdine in hypochlorhydric HIV-positive patients. *J. Acquir. Immune Defic. Syndr.* 24, 79–82.
- Shelton, M.J., Hewitt, R.G., Adams, J.M., Cox, S.R., Chambers, J.H., Morse, G.D., 2003. Delavirdine malabsorption in HIV-infected subjects with spontaneous gastric hypochlorhydria. *J. Clin. Pharmacol.* 43, 171–179.
- Sheppard, J.J., Mysak, E.D., 1984. Ontogeny of infantile oral reflexes and emerging chewing. *Child Dev* 55, 831–843.
- Simon, K., 2016. Colorectal cancer development and advances in screening. *Clin. Interv. Aging* 11, 967–976.
- Simonen, M., Dali-Youcef, N., Kaminska, D., Venesmaa, S., Kakela, P., Paakkonen, M., Hallikainen, M., Kolehmainen, M., Uusitupa, M., Moilanen, L., Laakso, M., Gylling, H., Patti, M.E., Auwerx, J., Pihlajamäki, J., 2012. Conjugated bile acids associate with altered rates of glucose and lipid oxidation after Roux-en-Y gastric bypass. *Obes. Surg.* 22, 1473–1480.
- Simons, C.C., Schouten, L.J., Weijnen, M.P., Goldbohm, R.A., van den Brandt, P.A., 2010. Bowel movement and constipation frequencies and the risk of colorectal cancer among men in the Netherlands Cohort Study on Diet and Cancer. *Am. J. Epidemiol.* 172, 1404–1414.
- Singh-Manoux, A., Gueguen, A., Ferrie, J., Shipley, M., Martikainen, P., Bonenfant, S., Goldberg, M., Marmot, M., 2008. Gender differences in the association between morbidity and mortality among middle-aged men and women. *Am. J. Public Health* 98, 2251–2257.
- Sjoberg, A., Lutz, M., Tannergren, C., Wingolf, C., Borde, A., Ungell, A.L., 2013. Comprehensive study on regional human intestinal permeability and prediction of fraction absorbed of drugs using the Ussing chamber technique. *Eur. J. Pharm. Sci.* 48, 166–180.
- Slavik, T., 2012. Human immunodeficiency virus-related gastrointestinal pathology: a southern Africa perspective with review of the literature (part 2: neoplasms and noninfectious disorders). *Arch. Pathol. Lab. Med.* 136, 316–323.
- Smit, C., De Hoogd, S., Brüggemann, R.J.M., Knibbe, C.A.J., 2018. Obesity and drug pharmacology: a review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. *Expert Opin. Drug Metab. Toxicol.* 14, 275–285.
- Smith, A., Henriksen, B., Cohen, A., 2011. Pharmacokinetic considerations in Roux-en-Y gastric bypass patients. *Am. J. Health-Syst. Pharm.* 68, 2241–2247.
- Smith, C.D., Herkes, S.B., Behrens, K.E., Fairbanks, V.F., Kelly, K.A., Sarr, M.G., 1993. Gastric acid secretion and vitamin B12 absorption after vertical Roux-en-Y gastric bypass for morbid obesity. *Ann. Surg.* 218, 91–96.
- Soldin, O.P., Mattison, D.R., 2009. Sex differences in pharmacokinetics and pharmacodynamics. *Clin. Pharmacokinet.* 48 (3), 143–157.
- Soldner, A., Christians, U., Susanto, M., Wacher, V.J., Silverman, J.A., Benet, L.Z., 1999. Grapefruit juice activates P-glycoprotein-mediated drug transport. *Pharm. Res* 16, 478–485.
- Somani, A.A., Thelen, K., Zheng, S., Trame, M.N., Coboeken, K., Meyer, M., Schnizler, K., Ince, I., Willmann, S., Schmidt, S., 2016. Evaluation of changes in oral drug absorption in preterm and term neonates for Biopharmaceutics Classification System (BCS) class I and II compounds. *Br. J. Clin. Pharm.* 81, 137–147.
- Spak, E., Björklund, P., Helander, H.F., Vieth, M., Olbers, T., Casselbrant, A., Lonroth, H., Fandriks, L., 2010. Changes in the mucosa of the Roux-limb after gastric bypass surgery. *Histopathology* 57, 680–688.
- Spiller, R., 2006. Role of motility in chronic diarrhoea. *J. Neurogastroenterol. Motil.* 18, 1045–1055.
- Standing, J.F., 2017. Understanding and applying pharmacometric modelling and simulation in clinical practice and research. *Br. J. Clin. Pharmacol.* 83, 247–254.
- Stappaerts, J., Annaert, P., Augustijns, P., 2013. Site dependent intestinal absorption of darunavir and its interaction with ketoconazole. *Eur. J. Pharm. Sci.* 49, 51–56.
- Stein, J., Makowiec, F., Starlinger, R.M., Caspary, W.F., 1999. Crohn's Disease. In: Caspary, W.F., Stein, J. (Eds.), *Darmkrankheiten*. Springer Verlag, Berlin, pp. 439–464.
- Stewart, K.D., Johnston, J.A., Matza, L.S., Curtis, S.E., Havel, H.A., Sweetana, S.A., Gelhorn, H.L., 2016. Preference for pharmaceutical formulation and treatment process attributes. *Patient Prefer. Adherence* 10, 1385–1399.
- Su, A., Gandhi, R., Barlow, C., Triadafilopoulos, G., 2017. A practical review of gastrointestinal manifestations in Parkinson's disease. *Parkinsonism Relat Dis* 39, 17–26.
- Su, Y.C., Wang, W.M., Wang, S.Y., Lu, S.N., Chen, L.T., Wu, D.C., Chen, C.Y., Jan, C.M., Horowitz, M., 2000. The association between *Helicobacter pylori* infection and functional dyspepsia in patients with irritable bowel syndrome. *Am. J. Gastroenterol.* 95, 1900–1905.
- Suchy, F.J., Brannon, P.M., Carpenter, T.O., Fernandez, J.R., Gilsanz, V., Gould, J.B., Hall, K., Hui, S.L., Lupton, J., Mennella, J., Miller, N.J., Osganian, S.K., Sellmeyer, D.E., Wolf, M.A., 2010. National institutes of health consensus development conference: lactose intolerance and health. *Ann. Intern. Med.* 152, 792–796.
- Sundaram, S.S., Bove, K.E., Lovell, M.A., Sokol, R.J., 2008. Mechanisms of disease: Inborn errors of bile acid synthesis. *Nature clinical practice. Gastroenterol. Hepatol.* 5, 456–468.
- Suri, A., Chapel, S., Lu, C., Venkatakrishnan, K., 2015. Physiologically based and population PK modeling in optimizing drug development: A predict-learn-confirm analysis. *Clin. Pharmacol. Ther.* 98, 336–344.
- Takagi, T., Ramachandran, C., Bermejo, M., Yamashita, S., Yu, L.X., Amidon, G.L., 2006. A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. *Mol. Pharm.* 3, 631–643.
- Tamargo, J., Rosano, G., Walther, T., Duarte, J., Niessner, A., Kaski, J.C., Cecconi, C., Drexler, H., Kjeldsen, K., Savarese, G., Torp-Pedersen, C., Atar, D., Lewis, B.S., Agewall, S., 2017. Gender differences in the effects of cardiovascular drugs. *Eur. Heart J* 3, 163–182.
- Tamboli, A.M., Todkar, P., Zope, P., FJ, S., 2010. An overview on bioequivalence: regulatory consideration for generic drug products. *J. Bioequiv. Availab.* 2, 86–92.
- Tamura, A., Shiomoto, T., Hachiya, S., Shigematsu, N., Hara, H., 2008. Low activities of intestinal lactase suppress the early phase absorption of soy isoflavones in Japanese adults. *Clin. Nutr.* 27, 248–253.
- Tang, L., Fatehi, M., Linsdell, P., 2009. Mechanism of direct bicarbonate transport by the CFTR anion channel. *J. Cyst. Fibros.* 8, 115–121.
- Tannergren, C., Bergendal, A., Lennernas, H., Abrahamsson, B., 2009. Toward an increased understanding of the barriers to colonic drug absorption in humans: implications for early controlled release candidate assessment. *Mol. Pharm.* 6, 60–73.
- Tatsuta, M., Iishi, H., Okuda, S., 1990. Gastric emptying in patients with fundal gastritis and gastric cancer. *Gut* 31, 767–769.
- Thaiss, C.A., Levy, M., Grosheva, I., Zheng, D., Soffer, E., Blacher, E., Braverman, S., Tengeler, A.C., Barak, O., Elazar, M., Ben-Zeev, R., Lehavi-Regev, D., Katz, M.N., Pevsner-Fischer, M., Gertler, A., Halpern, Z., Harmelin, A., Aamar, S., Serradas, P., Grosfeld, A., Shapiro, H., Geiger, B., Elinav, E., 2018. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. *Science* 359, 1376–1383.
- Thakkar, N., Salerno, S., Hornik, C.P., Gonzalez, D., 2017. Clinical Pharmacology Studies in Critically Ill Children. *Pharm. Res.* 34, 7–24.
- Thompson, C.M., Johns, D.O., Sonawane, B., Barton, H.A., Hattis, D., Tardif, R., Krishnan, K., 2009. Database for physiologically based pharmacokinetic (PBPK) modeling: physiological data for healthy and health-impaired elderly. *J. Toxicol. Env. Heal. B* 12, 1–24.
- Thompson, T., Lee, M.G., Clarke, T., Mills, M., Wharfe, G., Walters, C., 2012. Prevalence of gastrointestinal symptoms among ambulatory HIV patients and a control population. *Ann. Gastroenterol.* 25, 243–248.
- Thor, P., Lorens, K., Tabor, S., Herman, R., Konturek, J.W., Konturek, S.J., 1996. Dysfunction in gastric myoelectric and motor activity in *Helicobacter pylori* positive gastritis patients with non-ulcer dyspepsia. *J. Physiol. Pharmacol.* 47, 469–476.
- Tilg, H., Moschen, A.R., 2014. Microbiota and diabetes: an evolving relationship. *Gut* 63, 1513–1521.
- Tistaert, C., Heimbach, T., Xia, B., Parrott, N., Samant, T.S., Kesiosoglou, F., 2019. Food effect projections via physiologically based pharmacokinetic modeling: predictive case studies. *J. Pharm. Sci.* 108, 592–602.
- Tosetti, C., Corinaldesi, R., Stanghellini, V., Pasquali, R., Corbelli, C., Zoccoli, G., Di Febo, G., Monetti, N., Barbara, L., 1996. Gastric emptying of solids in morbid obesity. *Int. J. Obes. Relat. Metab. Disord.* 20, 200–205.
- Touw, D., Mouton, J., Vinks, A., Horrevorts, A., Heijerman, H., 2000. Antibiotic treatment in cystic fibrosis: Part I: Introduction: Clinical pharmacokinetics and toxicology. *Antimicrob. Infect. Dis. Newslett.* 18, 25–29.
- Tran, T.H., Smith, C., Mangione, R.A., 2013. Drug absorption in celiac disease. *Am. J. Health-Syst. Pharm.* 70, 2199–2206.
- Trumpi, K., Emmink, B.L., Prins, A.M., van Oijen, M.G., van Diest, P.J., Punt, C.J., Koopman, M., Kranenburg, O., Rinkes, I.H., 2015. ABC-transporter expression does not correlate with response to irinotecan in patients with metastatic colorectal cancer. *J. Cancer* 6, 1079–1086.
- Usai-Satta, P., Oppia, F., Lai, M., Cabras, F., 2018. Motility disorders in celiac disease and non-celiac gluten sensitivity: the impact of a gluten-free diet. *Nutrients* 10.
- Vaarala, O., Atkinson, M.A., Neu, J., 2008. The "perfect storm" for type 1 diabetes: the complex interplay between intestinal microbiota, gut permeability, and mucosal immunity. *Diabetes* 57, 2555–2562.
- Van Den Abeele, J., Rayyan, M., Hoffman, I., Van de Vijver, E., Zhu, W., Augustijns, P., 2018. Gastric fluid composition in a paediatric population: Age-dependent changes relevant for gastrointestinal drug disposition. *Eur. J. Pharm. Sci.* 123, 301–311.

- van der Galiën, R., Ter Heine, R., Greupink, R., Schalkwijk, S.J., van Herwaarden, A.E., Colbers, A., Burger, D.M., 2019. Pharmacokinetics of HIV-integrase inhibitors during pregnancy: mechanisms, clinical implications and knowledge gaps. *Clin. Pharmacokinet.* 58, 309–323.
- van Groen, B.D., van de Steeg, E., Mooij, M.G., van Lipzig, M.M.H., de Koning, B.A.E., Verdijk, R.M., Wortelboer, H.M., Gaedigk, R., Bi, C., Leeder, J.S., van Schaik, R.H.N., van Rosmalen, J., Tibboel, D., Vaes, W.H., de Wildt, S.N., 2018. Proteomics of human liver membrane transporters: a focus on fetuses and newborn infants. *Eur. J. Pharm. Sci.* 124, 217–227.
- Van Hartesveldt, C., Joyce, J.N., 1986. Effects of estrogen on the basal ganglia. *Neurosci. Biobehav. Rev.* 10, 1–14.
- van Oosterhout, J.J., Dzinjalama, F.K., Dimba, A., Waterhouse, D., Davies, G., Zijlstra, E.E., Molyneux, M.E., Molyneux, E.M., Ward, S., 2015. Pharmacokinetics of anti-tuberculosis drugs in HIV-positive and HIV-negative adults in Malawi. *Antimicrob. Agents Chemother.* 59, 6175–6180.
- Van Orten-Luiten, A.C.B., 2017. Food for the Aging Population, Food-Drug Interactions in Elderly, second ed. Woodhead Publishers.
- van Rongen, A., Brill, M.J.E., Vaughns, J.D., Väitalo, P.A.J., van Dongen, E.P.A., van Ramshorst, B., Barrett, J.S., van den Anker, J.N., Knibbe, C.A.J., 2018. Higher midazolam clearance in obese adolescents compared with morbidly obese adults. *Clin. Pharmacokinet.* 57, 601–611.
- Van Thiel, D.H., Gavalier, J.S., Joshi, S.N., Sara, R.K., Strempel, J., 1977. Heartburn of pregnancy. *Gastroenterology* 72, 666–668.
- Varela, J.E., Hinojosa, M., Nguyen, N., 2009. Correlations between intra-abdominal pressure and obesity-related co-morbidities. *Surg. Obes. Relat. Dis.* 5, 524–528.
- Vertzoni, M., Goumas, K., Soderlind, E., Abrahamsson, B., Dressman, J.B., Poulou, A., Reppas, C., 2010. Characterization of the ascending colon fluids in ulcerative colitis. *Pharm. Res.* 27, 1620–1626.
- Very, N., Lefebvre, T., El Yazidi-Belkoura, I., 2018. Drug resistance related to aberrant glycosylation in colorectal cancer. *Oncotarget* 9, 1380–1402.
- Vet, N.J., Brussee, J.M., de Hoog, M., Mooij, M.G., Verlaet, C.W., Jerchel, I.S., van Schaik, R.H., Koch, B.C., Tibboel, D., Knibbe, C.A., de Wildt, S.N., Skic, 2016. Inflammation and organ failure severely affect midazolam clearance in critically ill children. *Am. J. Respir. Crit. Care Med.* 194, 58–66.
- Vilela, E.G., Torres, H.O., Ferrari, M.L., Lima, A.S., Cunha, A.S., 2008. Gut permeability to lactulose and mannitol differs in treated Crohn's disease and celiac disease patients and healthy subjects. *Braz. J. Med. Biol. Res.* 41, 1105–1109.
- Villiger, A., Stillhart, C., Parrott, N., Kuentz, M., 2016. Using physiologically based pharmacokinetic (PBPK) modelling to gain insights into the effect of physiological factors on oral absorption in paediatric populations. *AAPS J* 18, 933–947.
- Virally-Monod, M., Tielmans, D., Kevorkian, J.P., Bouhnik, Y., Flourie, B., Porokhov, B., Ajzenberg, C., Warnet, A., Guillausseau, P.J., 1998. Chronic diarrhoea and diabetes mellitus: prevalence of small intestinal bacterial overgrowth. *Diabetes Metab* 24, 530–536.
- Wagner, C., Zhao, P., Arya, V., Mullick, C., Struble, K., Au, S., 2017. Physiologically based pharmacokinetic modeling for predicting the effect of intrinsic and extrinsic factors on darunavir or lopinavir exposure coadministered with ritonavir. *J. Clin. Pharmacol.* 57, 1295–1304.
- Wang, G., Agenor, K., Pizot, J., Kotler, D.P., Harel, Y., Van Der Schueren, B.J., Quercia, I., McGinty, J., Laferrere, B., 2012. Accelerated gastric emptying but no carbohydrate malabsorption 1 year after gastric bypass surgery (GBP). *Obes. Surg* 22, 1263–1267.
- Wangboonskul, J., White, N.J., Nosten, F., ter Kuile, F., Moody, R.R., Taylor, R.B., 1993. Single dose pharmacokinetics of proguanil and its metabolites in pregnancy. *Eur. J. Clin. Pharmacol.* 44, 247–251.
- Webber, L., Divajeva, D., Marsh, T., McPherson, K., Brown, M., Galea, G., Breda, J., 2014. The future burden of obesity-related diseases in the 53 WHO European-Region countries and the impact of effective interventions: a modelling study. *BMJ open* 4, e004787.
- Wegener, M., Borsch, G., Schaffstein, J., Luerweg, C., Leverkus, F., 1990. Gastrointestinal transit disorders in patients with insulin-treated diabetes mellitus. *Dig. Dis.* 8, 23–36.
- Whitehead, E.M., Smith, M., Dean, Y., O'Sullivan, G., 1993. An evaluation of gastric emptying times in pregnancy and the puerperium. *Anaesthesia* 48, 53–57.
- Wisen, O., Johansson, C., 1992. Gastrointestinal function in obesity: motility, secretion, and absorption following a liquid test meal. *Metabolism* 41, 390–395.
- Witkamp, R.F., van Norren, K., 2018. Let thy food be thy medicine....when possible. *Eur. J. Pharmacol.* 836, 102–114.
- Wolking, S., Schaeffeler, E., Lerche, H., Schwab, M., Nies, A.T., 2015. Impact of genetic polymorphisms of ABCB1 (MDR1, P-glycoprotein) on drug disposition and potential clinical implications: update of the literature. *Clin. Pharmacokinet.* 54, 709–735.
- Wollmer, E., Klein, S., 2017. A review of patient-specific gastrointestinal parameters as a platform for developing in vitro models for predicting the in vivo performance of oral dosage forms in patients with Parkinson's disease. *Int. J. Pharm.* 533, 298–314.
- Won, C.S., Oberlies, N.H., Paine, M.F., 2012. Mechanisms underlying food-drug interactions: inhibition of intestinal metabolism and transport. *Pharmacol. Ther.* 136 (2), 186–201.
- Wu, H.F., Hristeva, N., Chang, J., Liang, X., Li, R., Frassetto, L., Benet, L.Z., 2017. Rosuvastatin pharmacokinetics in asian and white subjects wild type for both OATP1B1 and BCRP under control and inhibited conditions. *J. Pharm. Sci.* 106, 2751–2757.
- Xavier, R.J., Podolsky, D.K., 2007. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 448, 427–434.
- Yang, Y., Carlin, A.S., Faustino, P.J., Motta, M.I., Hamad, M.L., He, R., Watanuki, Y., Pinnow, E.E., Khan, M.A., 2009. Participation of women in clinical trials for new drugs approved by the food and drug administration in 2000-2002. *J. Womens Health* 18, 303–310.
- Yoon, D.Y., Mansukhani, N.A., Stubbs, V.C., Helenowski, I.B., Woodruff, T.K., Kibbe, M.R., 2014. Sex bias exists in basic science and translational surgical research. *Surgery* 156, 508–516.
- Yu, B., Xie, J., 2016. Identifying therapeutic targets in gastric cancer: the current status and future direction. *Acta Biochim. Biophys. Sin.* 48, 90–96.
- Yung, D., Douglas, S., Hobson, A.R., Giannakou, A., Plevris, J.N., Koulaouzidis, A., 2016. Morpho-functional evaluation of small bowel using wireless motility capsule and video capsule endoscopy in patients with known or suspected Crohn's disease: pilot study. *Endosc. Int. Open* 4, E480–E486.
- Zacchi, P., Mearin, F., Humbert, P., Formiguera, X., Malagelada, J.R., 1991. Effect of obesity on gastroesophageal resistance to flow in man. *Dig. Dis. Sci.* 36, 1473–1480.
- Zahorska-Markiewicz, B., Jonderko, K., Lelek, A., Skrzypek, D., 1986. Gastric emptying in obesity. *Hum. Nutr. Clin. Nutr.* 40, 309–313.
- Zanger, U.M., Schwab, M., 2013. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol. Therap.* 138, 103–141.
- Zevin, A.S., McKinnon, L., Burgener, A., Klatt, N.R., 2016. Microbial translocation and microbiome dysbiosis in HIV-associated immune activation. *Curr. Opin. HIV AIDS* 11, 182–190.
- Zhong, H.J., Yuan, Y., Xie, W.R., Chen, M.H., He, X.X., 2016. Type 2 diabetes mellitus is associated with more serious small intestinal mucosal injuries. *PLoS One* 11, e0162354.
- Zimmermann, M., Zimmermann-Kogadeeva, M., Wegmann, R., Goodman, A.L., 2019. Mapping human microbiome drug metabolism by gut bacteria and their genes. *Nature* 570, 462–467.
- Zimmermann, T., Laufen, H., Yeates, R., Scharpf, F., Riedel, K.D., Schumacher, T., 1999. The pharmacokinetics of extended-release formulations of calcium antagonists and of amlodipine in subjects with different gastrointestinal transit times. *J. Clin. Pharmacol.* 39, 1021–1031.
- Zoppi, G., Andreotti, G., Pajno-Ferrara, F., Njai, D.M., Gaburro, D., 1972. Exocrine pancreas function in premature and full term neonates. *Pediatr. Res.* 6, 880–886.